Assessment report

Benlysta

International Non proprietary Name: belimumab

Procedure No. EMEA/H/C/002015

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Product information

Name of the medicinal product:	Benlysta
Marketing Authorisation Holder:	Glaxo Group Limited Glaxo Wellcome House Berkeley Avenue Greenford, Middlesex UB6 0NN United Kingdom
Active substance:	belimumab
International Non-proprietary Name:	belimumab
Pharmaco-therapeutic group (ATC Code):	Selective immunosuppressants (L04AA26)
Therapeutic indication:	Add-on therapy in adult patients with active autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy.
Pharmaceutical form:	Powder for concentrate for solution for infusion
Strengths:	120 mg and 400 mg
Route of administration:	Intravenous use
Packaging:	vial (glass)
Package size:	1 vial

Table of contents

List of abbreviations

aCl	anticardiolipin (antibody)
ACR	American College of Rheumatology
ADA	anti-drug antibodies
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine transaminase
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANOVA	analysis of variance
APTT	activated partial thromboplastin time
ARISg	Adverse Reaction Information System – Global (HGS safety database)
AST	aspartate transaminase
ATC	Anatomical Therapeutic Chemical classification system
BILAG	British Isles Lupus Assessment Group
BLyS	B lymphocyte stimulator protein
BLA	Biologics Licensing Application
BMI	body mass index
Bpm	beats per minute
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CCP	cyclic citrullinated peptide
CDIR	cytokine-dependent infusion reaction
CI	confidence interval
CL	total body clearance of drug
CMV	Cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CRD	controlled repeat dose
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
dL	Deciliter
DMARD	disease-modifying anti-rheumatic drug
DMC	data monitoring committee
DMID	Division of Microbiology and Infectious Disease
dsDNA	double-stranded deoxyribonucleic acid
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOP2	End of Phase 2
ER	emergency room
FDA	Food and Drug Administration
G	Gram
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
hERG	human ether-a-go-go related-gene
HGS	Human Genome Sciences
HLGT	high level group term
HLT	high level term
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HSR	hypersensitivity reaction
ICH	International Conference on Harmonization

Ig	Immunoglobulin
INN	International Nonproprietary Name
IS	Immunosuppressant
ITT	intention-to-treat
IU	international units
IV	Intravenous
Kg	Kilogram
LDH	lactic dehydrogenase
LLN	lower limit of normal
LLOQ	lower limit of quantification
LOD	limit of detection
LRTI	lower respiratory tract infection
Mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MITT	modified intent-to treat
mL	Milliliter
MMF	mycophenolate mofetil
mmHg	millimeters of mercury
MRT	mean residence time following intravenous dosing
MTX	Methotrexate
NMSC	non-melanoma skin cancer
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
PGA	Physician Global Assessment
PK	Pharmacokinetics
PT	prothrombin time
PTT	partial thromboplastin time
RA	rheumatoid arthritis
RBC	red blood cell (count)
RF	rheumatoid factor
RR	relative risk
SAE	serious adverse event
SC	Subcutaneous
SELENA	Safety of Estrogen in Lupus National Assessment
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SMQ	Standardised MedDRA Query
SNF	skilled nursing facility
SOC	system organ class
SS	Sjögren's syndrome
TNF	tumor necrosis factor
TQT	thorough QT
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States
USAN	United States Adopted Name
UTI	urinary tract infection
TK	Toxicokinetic
V_2	volume of distribution for the peripheral compartment
V_{ss}	volume of distribution at steady-state
WBC	white blood cell (count)
WHO	World Health Organization
WM	Waldenström's macroglobulinemia

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Glaxo Group Limited submitted on 4 June 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Benlysta, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication treatment of active, autoantibody-positive systemic lupus erythematosus (SLE).

The legal basis for this application refers to:
Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application
New active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/254/2009 for the following conditions:

- Systemic lupus erythematosus

On the agreement of a paediatric investigation plan (PIP), the granting of a deferral and the granting of a product-specific waiver.

- Systemic lupus erythematosus

The PIP is not yet completed.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 28 June 2006 and 30 May 2008. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Kristina Dunder** Co-Rapporteur: **Arantxa Sancho-Lopez**

- The application was received by the EMA on 4 June 2010.
- The procedure started on 23 June 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 September 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 September 2010.
- During the meeting on 21 October 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 October 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 December 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 January 2011.
- During the CHMP meeting on 17 February the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 March 2011.
- During a meeting of an ad hoc Expert group on 30 March 2011, experts were convened to address questions raised by the CHMP.
- During the meeting on 16-19 May 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Benlysta on 19 May 2011. The applicant provided on 19 April 2011 the letter of undertaking on the post-authorisation measures to be completed.

2. Scientific discussion

2.1. Introduction

Problem statement

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease which is characterized clinically by arthralgia, arthritis, skin rashes, serositis, hematologic abnormalities, central nervous system (CNS) dysfunction and renal inflammation. SLE is approximately 10 times more common in women than men, and more prevalent in African-Americans than Caucasians. The onset of disease is generally between 15 and 44 years of age.

Characteristic immunologic abnormalities include the presence of antinuclear antibodies (ANA), highly specific antibodies to double-stranded DNA (ds-DNA) and the Smith antigen (Sm) in serum. Patients often exhibit complement activation including the presence of circulating complement split products and depressed level of C3 and C4 complement in the serum.

Hydroxychloroquine and corticosteroids are currently licensed in the European Union (EU) for use in SLE; however, there have been no new therapies for the treatment of SLE approved in recent decades. Standard-of-care (SOC) therapy for SLE typically begins with antimalarials (e.g. hydroxychloroquine) that are often combined with corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) which help control mucocutaneous and joint involvement. Immunosuppressive or immunomodulatory agents such as azathioprine, leflunomide, methotrexate, mycophenolate mofetil, cyclophosphamide, and cyclosporine are also frequently used for the treatment of SLE, typically for more severe or more active disease that is not adequately controlled. For severe or refractory disease combinations of therapies are also commonly used.

The drugs used to treat SLE themselves are associated with additional risks and substantial adverse effects and complications. The chronic use of corticosteroids is associated with Cushingoid syndrome, increased risk of opportunistic infections, and the development of osteoporosis. The limitation of chronic use of CS is generally considered of great clinical value in SLE management. Thus, there is substantial unmet medical need for newer, more-effective and better-tolerated therapies for the treatment of SLE.

About the product

Benlysta contains belimumab as an active substance, a recombinant human IgG1λ monoclonal antibody that binds to and inhibits the biological activity of soluble human B-lymphocyte stimulator (BLyS). In humans, soluble BLyS is biologically active and produced primarily by monocytes and activated neutrophils. The primary function of BLyS is the promotion of B-lymphocyte survival and differentiation.

The expected pharmacologic effects of inhibiting BLyS in autoimmune disease such as SLE would be the reduction in selected B-cell subsets and autoantibodies and normalization of immunoglobulin and complement levels. The effects on these important biological markers of SLE activity are expected to be followed by clinical effects including reductions in disease activity, risk of flare, and steroid use.

The initially proposed indication for Benlysta was: "*Reducing disease activity in adult patients with active, autoantibody positive, systemic lupus erythematosus who are receiving standard therapy*".

The approved indication is: *"Benlysta is indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g positive anti dsDNA and low complement) despite standard therapy".*

The recommended dose regimen is 10 mg/kg Benlysta on Day 0, 14 and 28, and at 4-weeks intervals thereafter. The patient's condition should be evaluated continuously. Discontinuation of treatment with Benlysta should be considered if there is no improvement in disease control after 6 months of treatment.

Type of application and aspects of development

The clinical development program for Benlysta to support the efficacy in the treatment of SLE at the proposed dose of 10 mg/kg included one Phase 2 and two Phase 3 studies conducted in patients with active SLE.

Regulatory advice was received from the European Medicines Agency on clinical, non-clinical and CMC aspects of the development programme on 30th June 2006. Follow on scientific advice in relation to nonclinical and CMC issues was received on 30th May 2008.

There are currently no EMA/CHMP Guidelines for the clinical development of products in this indication.

A Paediatric Investigation Plan (PIP) was agreed for the condition systemic lupus erythematosus which is not yet complete. This includes a study in paediatric SLE patients from 5 to less than 18 years; a deferral for some or all studies contained in the PIP was agreed. For children from birth to less than 5 years a waiver was agreed.

2.2. Quality aspects

2.2.1. Introduction

The active substance belimumab is a human IgG1λ monoclonal antibody. Belimumab binds to soluble human B Lymphocyte Stimulator (BLyS), a B-cell survival factor, and prevents BLyS binding to its receptor on mature B-cells, thus inhibiting B-cell survival, including autoreactive B cells.

Benlysta is presented as a powder for concentrate for solution for infusion. One vial (single use) contains 120 mg or 400 mg of belimumab formulated with citric acid monohydrate, sodium citrate dihydrate, sucrose and polysorbate 80. Prior to administration, the 120 mg/vial and 400 mg/vial configurations should be reconstituted with 1.5 mL and 4.8 mL of sterile water for injections, respectively, resulting in 1.7 mL (1.5 mL deliverable) and 5.4 mL (5.0 mL deliverable), respectively, of reconstituted 80 mg/mL belimumab. The reconstituted solution is diluted to 250 ml with 0.9% normal saline for IV infusion.

2.2.2. Active Substance

Description of the active substance

Belimumab consists of 2 heavy chains, and 2 light chains of the lambda subclass. Each heavy chain contains 452 amino acid residues and each light chain contains 214 amino acid residues. There are 3 post-translational modifications: a conserved N-linked glycosylation on the CH2 domain of the heavy chain, the conversion of the N-terminal glutamine residue of the heavy chain into pyroglutamate, and loss of C-terminal lysine residue of the heavy chain.

Belimumab contains 32 cysteine residues (10 in the 2 light chains and 22 in the 2 heavy chains), all of which participate in 4 inter-chain disulfide bonds and 12 intra-chain disulfide bonds for a total of 16 disulfide bonds. Disulfide linkages in belimumab are identical to the native wild-type human IgG1 antibody.

Carbohydrates on the N-linked glycosylation site are core-fucosylated, biantennary, complex-type oligosaccharides, as expected from IgG1 antibodies produced from NS0 cell lines.

Manufacture

Belimumab is produced in a NS0 cell line using a serum-free production medium. The purification process comprises a series of chromatographic steps, viral inactivation and filtration steps, concentration/diafiltration and formulation. The purified bulk active substance is filled in storage containers and shipped to the finished product manufacturing site.

Development genetics
Belimumab is a human $IgG_1λ$ monoclonal antibody produced from a recombinant NS0 cell line stably transfected with the belimumab heavy chain and light chain genes.

Cell banking system
A two-tiered cell banking system of Master Cell Bank (MCB) and Working Cell Bank (WCB) was developed and maintained in accordance to cGMP and ICH guidelines.

Procedures followed for the preparation of MCB and WCB were described. An extensive range of tests was performed for their characterisation, in accordance with ICH guidelines, including identity, viability, stability, presence of adventitious agents.

Fermentation and purification process

Cell culture (serum-free production medium) and harvest processes occur in several stages that expand the cells followed by a production scale bioreactor stage, wherein belimumab accumulates in the bioreactor. After recovery of the belimumab containing supernatant, belimumab is purified by a series of chromatography and filtrations steps that includes inactivation and filtration of putative viruses. Belimumab is formulated with excipients at a specified concentration and filtered into bulk active substance containers.

Reprocessing is allowed after either viral filtration or bulk filtering.

Shipping to the fill-finish site is by a refrigerated truck (2-8°C) and typical shipping duration is 24 hours. Product temperature is maintained (≤ -40°C) during shipping. Shipping procedures are performed under validated conditions.

Process validation

Process validation studies were executed at both commercial- and small-scale. All small-scale validation studies, where appropriate, were performed subsequent to qualification studies that demonstrated the utility of the scale-down model. All assays used to generate data in support of process validation were either qualified or validated for their intended use. All non-compendial in-process control and bulk active substance release assays used for the analysis of conformance lots were validated and compendial assays were qualified.

Process validation activities for belimumab occurred under the direction of a Process Validation Master Plan. This document summarized the overall approach to process validation including sections on documentation, the role of process characterization, status of all assays used, scale of validation and a description of the intended studies that comprise upstream and downstream process validation.

Manufacturing process development

Several bulk active substance manufacturing processes were used during the course of development. The proposed commercial process supplied a portion of the Phase 3 clinical program. The main changes over the course of the manufacturing process development have been with respect to process scale, cell culture process mode, and cell bank used. Two formulations were used during the course of development. Material from each of the manufacturing processes and both formulations were used in nonclinical and clinical studies.

Conformance lots for the belimumab commercial manufacturing process validation were executed according to the manufacturing batch records, the cell culture and primary recovery process validation protocol, the purification process validation protocol, and the Process Validation Master Plan.

It was demonstrated that the process consistently maintains process parameters within specified ranges and meets pre-established acceptance criteria for performance indicators.

Characterisation

A) Elucidation of structure and other characteristics

A1) Physicochemical characterisation:
Physicochemical characterisation of belimumab active substance consists of a variety of state-of-the-art analytical procedures. The primary structure of belimumab was characterised with respect to its amino acid composition, monosaccharide composition, terminal sequences, complete sequence verification, disulfide linkage and post-translational modifications, including glycosylation and attached glycan structures. The overall integrity of the primary structure was assessed by peptide mapping and mass spectrometry. The secondary structure was evaluated by circular dichroism in the far UV region and Fourier Transform Infrared spectroscopy. The tertiary structure was evaluated by fluorescence spectroscopy, ultraviolet light spectroscopy (UV) and differential scanning calorimetry. Quaternary structure and hydrodynamic properties were evaluated by analytical ultracentrifugation (AUC).

Belimumab is an IgG_1 antibody which contains a conserved N-linked glycosylation site on the CH2 domain of each heavy chain at asparagine-303. Complete characterisation of the glycan distribution and glycan structures were given.

Product-related variants such as sialic acid, lysine, deamidation, oxidation variants were investigated.

A2) Biological characterisation:
The biological activity of belimumab is assessed via its interaction with soluble BLyS in an in vitro cell based binding assay.

The *in vitro* binding characteristics of belimumab have been assessed using solid-phase ELISA, quantitative binding analyses, flow cytometric analyses, and cell-based functional assays.

B) Impurities
Potential process-related impurities include cell substrate derived impurities (host cell proteins, host cell DNA), media components, downstream-derived impurities.

Product-related impurities include aggregates, fragments and crosslinked variants (covalent crosslinks of light to heavy chains).

Product-related substances include the following variants: lysine, deamidation, sulfhydryl groups, methionine oxidation.

Stability

The design of the stability program, including the testing intervals and temperature storage conditions, are in accordance with current guidelines. The tests chosen are a subset of tests from the release specifications selected for stability-indicating properties.
The stability data provided were within the specifications and support the proposed shelf life for the active substance when stored at ≤-40°C protected from light.

In accordance with EU GMP guidelines, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3. Finished Medicinal Product

Pharmaceutical Development
Belimumab active substance is formulated with citric acid monohydrate, sodium citrate dihydrate, sucrose and polysorbate 80.

There is no overage of drug substance in the belimumab dosage form or overage in the manufacture of the drug product.

The drug product manufacturing process evolved during clinical development based on the product formulation, the required scale of manufacturing, the container closure configuration appropriate for progressing through clinical development, and the manufacturing site selected for manufacture of the finished product. Changes included new manufacturing facilities, change to the bulk active substance container, change to the finished product formulation before initiating Phase 3 clinical studies, change to the drug product concentration, fill volume, vial size and lyophilisation cycle parameters.

Adventitious agents

Serum-free and animal source-free media are used throughout the master cell bank and working cell bank preparation, and the manufacturing process. Several raw materials are derived from plant sources. Two cell culture raw materials contain components derived from animal origins.
The TSE risk evaluation is acceptable and in line with Note for Guidance on "Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Products" (EMA/410/01 Rev. 2).

The belimumab end-of-production cell line is deemed to be free of adventitious agents and microbial contamination. However, as expected for a NS0 cell line, retrovirus-like particles are detected in the cell bank. The level though is within the virus removal capacity of the purification process.

The manufacturing process effectively removes enveloped and non-enveloped viruses as shown in the presented virus clearance studies. The results were considered acceptable.

Risk assessment calculations were made based on the results of the viral clearance study with the XMuLV as model virus. The results were considered acceptable.

The viral safety of the product has been studied in line with ICH Q5A guideline. The results obtained were considered satisfactory and show a good viral safety profile for the product.

Manufacture of the product

The finished product manufacturing process comprises several steps, including dilution of the bulk active substance, filtration steps, sterile filtration (0.22 µm), filling into Type I glass vials and partial stopper placement (latex-free, siliconised rubber), lyophilisation and stoppering, sealing (flip-off aluminium), capping, inspection of vials, labelling and packaging.

For process validation, conformance lots were manufactured at commercial scale. They met acceptance criteria as defined in the validation protocol, demonstrating that the manufacturing process is robust and consistently yields product capable of meeting pre defined quality characteristics. The finished product manufacturing, including lyophilisation, transport and holding times, was considered sufficiently validated.

Stability of the product

Real-time and accelerated stability studies were initiated in accordance with ICH guidelines and per protocol to monitor the time-temperature stability of cGMP lots of the finished product. On the basis of the data provided, the proposed shelf life for the finished product is 36 months at 2-8°C.

In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

No Major Objection on Quality aspects was identified during the evaluation of Benlysta.

Active substance
The procedures applied for the establishment of the master and working cell banks were adequately described. The cell banks were extensively and adequately characterised.

The active substance manufacturing process is standard for this class of products and is considered state of the art. It is well defined and the controls in places have been adequately justified and are considered appropriate.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

Reprocessing is supported by data from a small scale validation study showing that quality was not compromised by one additional filtration. The applicant committed to monitor the first reprocessed commercial batch according to the commercial cGMP stability protocol.

The active substance commercial manufacturing process has been carefully validated with respect to all relevant parameters and good consistency has been shown.

Several early manufacturing processes were used during the course of process and clinical development. The whole development process is well described with changes presented sequentially. Comparability studies have been performed to demonstrate that the changes had no major impacts on the quality of belimumab active substance. A bridging pharmacokinetic study in vivo was performed to complement the comparability study.

Belimumab was extensively characterised using state-of-the-art methods, resulting in a detailed description of belimumab antibody, product-related substances and impurities as well as process-related impurities. The details of the characterisation demonstrated a well documented substance of high quality with low levels of impurities/related substances. Glycosylation of the antibody was also described in detail revealing common mouse patterns with a N-linked glycosylation site on the heavy chain. Apart from the usual variants G0, G1 and G2, other non-human glycosylation was detected.

Although the applicant claimed that the mechanism of action of belimumab does not involve the Fc region, it was considered necessary to perform a functional characterisation to determine the contribution of this part of the molecule.

A subset of the characterisation tests were chosen for release control. The proposed test panel is extensive and includes most relevant critical quality attributes. However, it was proposed to include additional tests for the control of belimumab active substance.

Long-term stability studies support the proposed shelf-life when stored at ≤-40°C protected from light.

Viral safety and safety concerning other adventitious agents including TSE are sufficiently assured

A pre-approval inspection was conducted at the proposed manufacturing facilities. EU-GMP compliance of these facilities was confirmed.

Finished product

Pharmaceutical development of the finished product has been adequately described.

The finished product manufacturing process is well described and adequately validated.

Several minor changes were made to the process between the early clinical phase (Phase 1/2), Phase 3 including a change of formulation buffer. In addition, during Phase 3 and in preparation for commercial production, the lyophilization process was scaled up.

All non compendial analytical methods have been validated and are the same as those used for release of the active substance. Compendial methods used for release of the finished product have been qualified (most of them also used for the drug substance). Control of finished product was considered appropriate.

The proposed shelf-life of 36 months at 2-8°C for the finished product is supported by the provided stability data.

In-use stability studies were conducted. The total time from reconstitution of Benlysta to completion of infusion should not exceed 8 hours. In addition, belimumab finished product is compatible with polyvinylchloride and polyolefin IV bags containing normal saline with tubing for intraveneous delivery; but it is not compatible with 5% dextrose IV diluent solution. The use of an in-line filter or peristaltic pump was shown to have no impact on product quality.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Viral safety and safety concerning other adventitious agents including TSE have been sufficiently assured. CHMP recommended addressing a number of points post-approval.
The overall Quality of Benlysta is considered acceptable.

2.3. Non-clinical aspects

2.3.1. Introduction

Belimumab is a human IgG1λ monoclonal antibody that specifically binds to soluble human B Lymphocyte Stimulator (BLyS), a B-cell survival factor, and prevents BLyS binding to its receptor on mature B-cells, thus inhibiting B-cell survival.

The nonclinical program for belimumab was conducted with consideration of the applicable recommendations given in the International Conference on Harmonisation (ICH) and CHMP guidance documents, with specific consideration of ICH S6 (Preclinical safety evaluation of biotechnology-derived pharmaceuticals) guideline. Regulatory advice was received from the European Medicines Agency on the development programme.

The primary pharmacodynamics of belimumab has been addressed in a series of studies *in vitro* and in mice *in vivo*. In addition, the repeated dose toxicology studies in monkeys included pharmacodynamic measures related to the pharmacological mechanism of belimumab.

The proposed commercial final finished product is a sterile, lyophilized powder to be reconstituted with sterile water for injection (WFI), for intravenous infusion. The product is to be diluted in normal saline and administered by intravenous (IV) infusion over 1 hour.

The pivotal preclinical studies were conducted in compliance with GLP. The other preclinical studies were conducted in accordance with GLP principles.

Throughout the dossier, belimumab is also referred to as GSK1550188 or HGS1006.

2.3.2. Pharmacology

BLyS Biology

B-lymphocyte stimulator protein (BLyS), the target of belimumab, is a cytokine and member of the tumour necrosis factor (TNF) ligand family and a potent stimulator of B-lymphocytes. The BLyS gene encodes a 285 amino acid, type II membrane-bound protein expressed on cells of myeloid origin, including normal monocytes, macrophages, and dendritic cells (Moore et al, 1999; Schneider et al, 1999). Cleavage of membrane-bound BLyS results in a soluble 152 amino acid BLyS protein, and the

predominant biologically active BLyS is a 51 kDa homotrimer consisting of three 152 amino acid peptide chains.

BLyS has been shown to bind three membrane bound receptors: transmembrane activator and CAML-interactor (TACI), B cell maturation antigen (BCMA), and B cell activating factor belonging to TNF family-receptor (BAFF-R)/BLyS receptor-3 (BR3), localized primarily on B lymphocytes (Gross et al, 2000; Xia et al, 2000; Yan et al, 2000; Yan et al, 2001b; Thompson et al, 2001).

The biological activity of BLyS coupled with the knowledge that BLyS is upregulated in patients with SLE provided the rationale for the development of belimumab as a therapy for SLE. *Ex vivo* studies with serum and synovial fluid from autoimmune patients have demonstrated that BLyS levels in autoimmune patient populations are significantly higher than those observed in normal healthy controls. Elevated BLyS levels have been found to be positively correlated with elevated anti dsDNA, IgG, and SLE disease activity. Therefore, belimumab by antagonizing BLyS activity and inhibiting BLyS-induced stimulation of B lymphocyte proliferation and antibody secretion, may provide therapeutic benefit in the treatment of autoimmune diseases such as SLE.

Primary pharmacodynamic studies

The expression profile of BLyS was assessed by Northern blot and flow cytometric analyses. BLyS in the form of a single 2.6 kb mRNA was readily detected in human PBMC (human peripheral blood mononuclear cells), spleen, lymph node, and bone marrow with lower, but detectable expression in placenta, heart, lung, fetal liver, thymus and pancreas. BLyS mRNA was also detected in HL-60 and K-562 monocytic cell lines. In summary, cell-surface BLyS expression was detected only on cells of monocytic/myeloid origin including HL-60, K-562, and THP-1 cells.

BLyS binding was detectable only on CD20+ cells, indicating that BLyS receptors are found on B cells but no on the other lineages. The studies also showed that BLyS receptor expression levels are comparable between human, monkey and mouse PBMC. BR-3 is generally considered the main receptor for BLyS and is first expressed on immature B cells through the activated B-cell stage, but is downregulated on plasma cells which instead express BCMA.

The potential of belimumab to bind to the membrane bound form was assessed in K-562 cells (human chronic myelogenous leukemia) and on human PBMCs. Belimumab showed no binding to membrane bound BLyS in these experiments.

Belimumab binds to soluble BLyS with high affinity and possesses a slow dissociation rate. This was shown by ELISA and BIAcore technology. The binding affinity to human BLyS showed a Kd value of about 0.2 nM and similar affinity was seen to monkey BLyS. In addition, belimumab was also demonstrated to bind to mouse BLyS but with a 10-fold lower affinity as compared to human and monkey BLyS. Belimumab was shown to be specific for binding to BLyS but not to other TNF ligand members (APRIL, TL1A, LIGHT, TNFα, TNFβ, FasL).

Belimumab was able to inhibit BLyS-BLyS receptor interaction for all three specific human BLyS receptors (TACI, BR3 and BCMA) with IC_{50} values ranged from 52 to 97 nM. The downstream effects of this inhibition include decreased splenocyte and tonsillar B-cell proliferation and decreased immunoglobulin levels, which were also shown in vitro. The *in vivo* studies in mice as well as in monkeys demonstrated that belimumab inhibits splenocyte proliferation and decreased the number of B-cells in spleen, lymph node and circulating B cells.

In a central scientific advice, it was requested that the Applicant provided data on the binding of belimumab to soluble and membrane bound BLyS in cynomolgus monkeys, to fully characterise the relevance of monkey as a model used in the preclinical studies. The Applicant has provided data

showing almost identical affinity of belimumab for human and cynomolgus soluble BLyS and similar pharmacological effects in monkeys and humans.

Secondary pharmacodynamic studies

Tissue cross-reactivity

A tissue binding study was performed to evaluate the potential cross-reactivity of belimumab with a panel of human and monkey tissues (for details see section on Tissue cross reactivity study below). The absence of belimumab tissues cross-reactivity in this study suggests that there is a limited chance of belimumab to produce secondary pharmacology as a result of off-target tissue binding.

No further studies were conducted to specifically investigate secondary pharmacodynamic effects of belimumab.

Safety pharmacology programme

No specific safety pharmacology studies were conducted due to the high specificity of belimumab for its target. In accordance with the Guideline CHMP/ICH/539/00, the Applicant included safety pharmacology assessments in three GLP studies in cynomolgus monkeys. In each of these studies, belimumab was generally safe and well tolerated and no abnormalities were attributable to belimumab. No changes in general behavioural, clinical observations or respiration were noted in any of the three studies that raised any specific cause for concerns. Therefore, the Applicant's justification for not performing a specific safety pharmacology study was considered acceptable.

Pharmacodynamic drug interactions

Belimumab is a monoclonal antibody with high specificity and affinity, and hence no non-clinical studies were undertaken to examine potential pharmacodynamic drug interactions. However, the Phase 2 and Phase 3 clinical trials in patients with SLE were designed to evaluate belimumab in the setting of standard of care therapy for SLE. In these trials, subjects received a wide range of concomitant SLE medications including corticosteroids, anti malarials, and other immunosuppressants (e.g., methotrexate or mycophenolate mofetil (MMF)). Special attention was paid to the incidence of adverse events (AE) that may be related to enhanced immunosuppression such as infection and cancer. AEs in subjects with baseline use of prednisone and immunosuppressants were generally comparable between placebo and belimumab treatment groups (see Clinical aspects).

2.3.3. Pharmacokinetics

Levels of belimumab in serum from mice and monkeys were measured by enzyme linked immunosorbent assays (ELISAs). Initially, the pharmacokinetic (PK) ELISA assay for analysing belimumab in serum was not validated. However, the later validated method showed comparable values of PK parameters in later studies as determined in the early PK studies. This was considered acceptable for CHMP.

The pharmacokinetics of belimumab following single intravenous (IV) administration to cynomolgus monkeys were shown to be biphasic and dose proportional over the range of doses tested (up to 150 mg/kg) and there were no significant differences in the serum concentrations between males and females. The mean steady-state volumes of distribution (V_{ss}) in monkeys range from 67-126 ml/kg which is in agreement with the low volume of distribution seen in humans (69-112 ml/kg). This is less than the extracellular fluid volume (170-210 ml/kg including plasma), indicating that belimumab localizes primarily in the plasma compartment and the interstitial fluid spaces of more permeable

tissues. Likewise the CL in human and monkey was low (5.5-7.3 ml/kg/day) indicating little clearance by renal routes as judged in relation to the glomerular filtration rate (monkeys~3000 ml/kg/day, Schaer et al, 1990; Davies and Morris, 1993). The terminal half life was long, ranging from 7 to 16 days in monkeys and from 8.5 to 14 days in humans. Toxicokinetic parameters measured following intravenous repeat dosing were comparable to those derived from the IV single dose studies and no apparent gender-related differences in exposure were observed following repeated IV dosing.

Detectable, treatment emergent anti-belimumab antibodies were identified in 12 out of 124 monkeys across nonclinical studies. Of these, 6 monkeys had reduced belimumab serum concentrations. Since the method for detecting antibodies was impacted of belimumab in the serum, the presence of an altered PK profile was used as an indirect measure of the presence of neutralizing antibodies.

Given the biological nature of belimumab, no studies of metabolism and excretion have been performed. Generally the expected consequence of metabolism of monoclonal antibodies is the degradation to small peptides and individual amino acids. Accordingly, biotransformation studies are not needed. The applicants justification for the absence of data on metabolism and excretion was acceptable for CHMP and in accordance with the note for guidance on the preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6; CPMP/ICH/302/95).

In reproductive toxicity studies in cynomolgus monkeys, belimumab was detected in infant umbilical cord blood at approximately ¼ of the levels in maternal serum on GD150, showing that belimumab is able to cross the placenta. About 180 days after birth belimumab was no longer detectable in infant serum. Belimumab was also detected in a few samples of milk indicating that belimumab is excreted in breast milk and might thus be transferred to the suckling infant.

The cynomolgus monkey was determined as the most relevant species for toxicology studies based on both pharmacology and pharmacokinetic studies. The pharmacokinetic data in monkeys indicated no significant difference in systemic exposure and pharmacokinetic parameters compared to humans. Furthermore, there were no significant different in the systemic exposure of non-pregnant or pregnant animals.

2.3.4. Toxicology

Choice of animal species

The non-clinical toxicology program supporting belimumab development has been performed exclusively in the cynomolgus monkey (*Macaca fascicularis*) based on the following reasons:

- The epitope for belimumab is preserved in cynomolgus monkey B lymphocyte stimulator (BLyS), and belimumab has a similar pharmacological activity and tissue cross-reactivity profile in cynomolgus monkeys and in humans.
- There is a high degree of homology between cynomolgus monkey and human BLyS, with 96.4% amino acid identity across the full-length protein, and 98% amino acid identity in the cleaved soluble portion of BLyS, which constitutes the biologically active form of BLyS.
- Belimumab binds human and cynomolgus monkey soluble BLyS with nearly identical affinity.
- The BLyS-BLyS receptor system appears to be comparable between cynomolgus monkeys and humans based on the fact that CD20+ B lymphocytes from cynomolgus monkeys express BLyS receptors at levels comparable to those on human B lymphocytes and that belimumab has the expected pharmacologic activity of specifically decreasing B lymphocytes in vivo.

- A tissue cross reactivity study of belimumab indicates that non-specific binding of belimumab to non-target tissues is likely to be limited in both humans and cynomolgus monkeys.

In addition, the Applicant considered that conducting the toxicology program in the single species of cynomolgus monkey is justified based on the absence of other suitable animal models. Belimumab administration in non-primates, i.e. mice, guinea pigs and rabbits, is not well tolerated. Although belimumab binds mouse BLyS, it does so with a 10-fold lower affinity for murine BLyS compared with belimumab binding to human or cynomolgus monkey BLyS. Moreover, multiple injections of belimumab in mice led to a strong anti-drug antibody response that altered the PK and in some cases led to death by an anaphylactoid–like response.

Single dose toxicity

Specific single dose toxicity studies were not conducted which is consistent with the ICH guidance regarding this type of substances. Non-clinical single dose PK studies of belimumab were performed in cynomolgus monkeys at doses up to 150 mg/kg, where no acute toxicity were observed (see Pharmacokinetic section).

Repeat dose toxicity

The toxicology of repeat IV administration of belimumab was assessed in two GLP toxicology studies in cynomolgus monkeys of 4 weeks and 6 months duration, respectively. Furthermore, a dose-tolerance study was conducted to determine the tolerability and potential toxicity of belimumab in non-pregnant female cynomolgus monkeys. The details of these studies including their major findings are summarized in the following table.

Table. Repeated dose toxicity studies in cynomolgus monkeys.

Study ID	GLP	Species/Sex/ Number/Group	Dose/Route (mg/kg)	Duration	NOEL (mg/kg/ day)	Major findings
Repeated dose toxicity study	Yes	Cynomolgus monkey 5M + 5F	0, 5, 15, 50 weekly/IV	4 wks + 4 wks recovery	< 5 mg/kg	**5 mg/kg:** [1]Lymphoid depletion of B cells [1]B-lymphocytes ↓ T cells ↑ Thyroid follicular epithelial degeneration 1/10 **50 mg/kg:** [1]Lymphoid depletion of B cells [1]B-lymphocytes ↓ T cells ↑ Thyroid follicular epithelial degeneration 5/10, IgA levels ↓ Splenic abscess 1/10 LN granuloma 1/10
Repeated dose toxicity study	Yes	Cynomolgus monkey 8M+8F	0, 5, 15, 50 2x/mo/IV	6 mo + 8 mo recovery	< 5 mg/kg	**All belimumab treated groups:** Total and mature B-lymphocytes ↓ [1]Spleen weight ↓ [1]Lymphoid follicle size ↓ (in spleen and mesenteric lymph nodes due to B cell reduction) Thyroid follicular epithelial degeneration in all groups including controls.
Dose finding	No	Cynomolgus monkey 3F	D1: 121 mg/kg D4: 97 mg/kg D15: 125 mg/g IV	15 d	125 mg/kg	There were no findings indicative of an adverse effect of belimumab. The target C_{max} of approx 3700 µg/mL was achieved after the 3rd dose.

[1] B cell reduction is due to pharmacological effect of belimumab treatment

The dosing frequency of weekly and biweekly IV administrations was a little more frequent than the proposed dosing regimen in the clinical setting. The highest dose used in the 4 week study provided an exposure margin of 5 with regard to C_{max} and 12 with regard to AUC. Aside from effects associated with the pharmacological activity of belimumab, there were few noteworthy findings in the toxicology studies indicating a low potential for toxicity. Most of the findings in the toxicity studies were reversible and could be related to the pharmacological effect of belimumab. However, a fairly uncommon finding, namely thyroid follicular epithelial degeneration, was seen in both toxicology studies and the reason for this observation is unclear. Given the even distribution of the observations among all the treatment groups including controls in the long term study, a treatment related effect seems not likely.

Extensive immunophenotyping evaluations in belimumab treated monkeys demonstrated that aside from the reductions in B cell counts, the number of other immunological cell types including T cells and NK cells are not significantly affected by belimumab treatment. A decrease in the B cells would expect a decrease in immunoglobulin levels but this was not that obvious in monkeys as was seen in SLE patients administered belimumab. Long-term toxicology studies in cynomolgus monkeys do not indicate an increased risk of infection or malignancy with belimumab. However, two monkeys treated with 50 mg/kg of belimumab during 4 weeks had necropsy findings (one abscessed spleen and one necrotizing granuloma in a lymph node) that may have been associated with infection and which could not be ruled out as a treatment related effect.

The Applicant was asked to provide the rationale for selection of 50 mg/kg as the high dose in the 4 week and 6 months repeated dose studies. The Applicant confirmed that the doses selected for the repeat dose toxicity studies were based on the intended pharmacological effect and at all dose levels evaluated complete saturation of all circulating BLyS, the maximum intended pharmacological effect, was achieved.

Development of anti-belimumab antibodies.

In the 4 weeks toxicity study, anti-belimumab antibodies were detected in one mid-dose (15 mg/kg) and two high-dose (50 mg/kg) monkeys, with one of the high-dose responses being borderline positive. Anti-belimumab antibodies did not alter the toxicokinetic of belimumab in affected monkeys in the present study, suggesting the absence of neutralising antibodies.

In the 6 months study anti-belimumab antibodies were detected in one low dose and one high dose monkey at Weeks 13 and 26, respectively, with reversal by week 52 during the recovery period; this was associated with increased clearance of belimumab in these two monkeys.

Genotoxicity

No genotoxicity studies were conducted. Belimumab is a monoclonal antibody and is not expected to interact directly with DNA or other chromosomal material. Regulatory guidance is consistent with studies on genotoxicity not being necessary for this type of product.

Carcinogenicity

No carcinogenicity studies have been conducted with belimumab. The Applicant has justified this approach with the following considerations:

- A traditional rodent carcinogenicity study would be limited due to rapid formation of anti-drug-antibodies to both belimumab and a homologous hamster anti-mouse BLyS antibody.
- A study in BLyS knockout mice for pre-neoplastic changes would not be a representative model as mice deficient in BLyS or the main BLyS receptor B3, have severely depleted numbers of peripheral B cells while belimumab treatment in humans reduces peripheral B cell populations by 50% but does not deplete them.
- No proliferative or pre-neoplastic changes were reported in any of the monkeys in a 6 month repeat dose toxicity study.

CHMP concurred with the Applicant's argumentation that the potential risk for malignancy with belimumab can only be evaluated in a clinical setting; the proposal for a clinical post-marketing safety study was supported.

Reproduction Toxicity

No specific studies on the effects of belimumab on fertility and early embryonic development were conducted. The reproductive organ/tissues were assessed in the 6 months repeat dose toxicology study and there were no indications that belimumab had an adverse effect on reproductive organs. In this study, increased testicular and epididymal weights, consistent with ongoing spermatogenesis, were observed in 3/6, 5/8, 5/8 and 3/8 male monkeys administered vehicle or 5, 15 and 50 mg/kg belimumab, respectively. Immature testes were observed in the remaining male monkeys. The presence of active or immature testes was correlated with body weight.

No microscopic abnormalities were noted in the testes, epididymides, prostate or seminal vesicles of any of the monkeys undergoing active spermatogenesis. Periodic vaginal discharges, consistent with actively cycling ovaries, were observed in 3/6, 7/8, 5/8 and 6/8 female monkeys administered vehicle or 5, 15 and 50 mg/kg belimumab, respectively. Hypoplasia of germinal cells was reported in both ovaries at the recovery necropsy (Week 60) of one female treated with belimumab at 15 mg/kg. Despite a decrease in the number of germinal cells, normal follicular maturation was present in both ovaries. A single 3 mm cyst was observed macroscopically in the left oviduct.

In a reproductive toxicity study in cynomolgus monkeys combining maternal, fetal and neonatal toxicity evaluations, belimumab was administered intravenously to a total of 45 pregnant female monkeys at a dose of either 5 mg/kg (25 animals) or 150 mg/kg (20 animals); twenty-one control animals received vehicle formulation only. The administration of belimumab started on gestation day 20 (GD20) and continued every 2 weeks up to GD150 or day of parturition. The systemic exposure in terms of AUC corresponded to exposure margins of 6 to 9 during gestation. The pharmacodynamic effects in terms of decreased total and mature B-lymphocytes were seen at GD90 and GD140 in all groups including controls. There was, however, a larger reduction in the belimumab treated groups.

An overall higher incidence of fetal losses in the combined treatment groups compared to controls (20% versus 14.3%) was seen in the study. Three cases of infant death were also seen in the treatment groups (11%) but no case in the control group. The overall incidence of fetal loss and infant dead are consistent with historical control data in monkeys 17, 8% (abortions/still born) and 10-12% (infant deaths). It cannot be concluded that the apparent increases in abortions, stillbirth and infant losses are resulting from treatment with belimumab. However, given the high spontaneous occurrence of these events, this model is insensitive to reveal minor or moderate effects on fetal/infant survival.

Toxicokinetic data

The toxicokinetics (TK) of belimumab after repeat dosing were evaluated in cynomolgus monkeys in toxicology studies and in a maternal, fetal and neonatal study. The TK of belimumab were dose-proportional following 4 weekly intravenous doses over the range of doses tested (5, 15 and 50 mg/kg), and there were no apparent differences between male and female monkeys (see table below). In addition, the TK parameters agreed well with the parameters obtained in the single dose studies. The mean concentration of belimumab 24 hours after the 4th weekly dose was approximately 1.9 times the mean concentration 24 hours after the 1st dose, consistent with the extent of accumulation expected based on weekly administration of a molecule with a half life of 14 days.

Toxicokinetic parameters and exposure multiples to human exposure

Study	**Dose (mg/kg/)**	**Animal C_{max} (µg/mL)**	**Animal AUC_{0-28d} (day.µg/ml)**	**Animal:Human[1] ratio Exposure Multiple**	
		M+F	**M+F**	**C_{max}**	**AUC**
4 wk repeat dose toxicity study [cynomolgus monkey]	5 15 50 weekly	153±9.0 472±21.8 1713±142	2868±259 9459±1000 37145±3671	0.5 1.5 5.5	0.9 3 12
reproductive toxicity study [cynomolgus monkey]	5 150 2x/month	192±25 5241±894	1041±148* 27441±4365*	0.6 17	0.33 9

[1] Human exposure corresponded to a C_{max} of 313 µg/mL and an AUC of 3083 µg.h/ml after dosing of 10 mg/kg (HGS 1006-POPPK). *AUC $_{0-14d}$ (week 17)

Local Tolerance

A local tolerance study of subcutaneously administered belimumab in cynomolgus monkey was conducted to support clinical studies evaluating the SC route of administration of belimumab. In this study minimal dermal irritations without any inflammatory reactions on the injection site were observed after subcutaneous (SC) administration of belimumab 25 mg/kg.

Intravenous administration showed no signs of dermal irritation as assessed in the repeated dose toxicity studies. No specific cause of concern emerged with regard to local tolerance of belimumab.

Other toxicity studies

Antigenicity/Immunogenicity

In addition to the assessment of anti-belimumab antibodies in the repeat dose toxicity studies, immunogenicity of belimumab was also assessed in a dedicated 22-week subcutaneous immunogenicity study in order to support clinical studies evaluating the subcutanous administration of belimumab. Immunogenicity, TK and pharmacodynamics of SC administration of 1 mg/kg of belimumab either 2 or 4 times a week via SC injection over a duration of 13 weeks were evaluated. Study endpoints included mortality, clinical signs, clinical pathology, TK evaluations, immunophenotyping, and immunogenicity results.

Table. Immunogenicity study in cynomolgus monkey after SC administration of belimumab

Study	Species/Sex/ Number/Group	Dose/ Route	Duration	Major findings
22-week SC immuno-genicity study	Cynomolgus monkey 5 M + 5 F/group	0 mg/kg 1 mg/kg (2x/w) 1 mg/kg (4x/w) sc	13 weeks (followed by 9 weeks of treatment free period)	Belimumab significantly reduced the number of peripheral blood B cells (CD20+) in both dose groups. Specific anti-belimumab antibodies were identified in 1 serum sample from 1 monkey; samples collected before and after the positive Day 71 sample were not confirmed to be positive in this monkey. The TK profile observed for this animal did not appear to be altered. No apparent gender-related differences in exposure were observed.

All animals survived the scheduled in-life phase and were then sacrificed. No necropsy was conducted. No test article-related effects on clinical signs, food consumption or body weight were observed. All animals that received belimumab had systemic exposure to belimumab at the expected level through the dosing and treatment-free periods.

In summary, across all studies, detectable, treatment emergent anti-belimumab antibodies have been identified in 12 out of 124 monkeys. Of these, 6 monkeys had reduced belimumab serum concentrations. Since the method for detecting antibodies was impacted of belimumab in serum, the presence of an altered PK profile was used as an indirect measure of the presence of neutralizing antibodies.

Tissue-cross reactivity study

A tissue cross reactivity study was conducted to identify any potential off-target binding of belimumab to human and cynomolgus monkey tissue. Cryosections of thirty-five human tissues (each from a minimum of 3 individuals) and 34 cynomolgus tissues (each from a minimum of 2 monkeys) were stained immunohistochemically with 2 and 10 µg/ml belimumab. Cryosections of pelleted and frozen BLyS-transfected human embryonic kidney (HEK)293 cells were used as a positive control for the immunohistochemical staining procedure and HEK293 cells transfected with vector control (no BLyS) were used as a negative control. Evaluation of cynomolgus monkey thyroid tissue was also performed at higher antibody concentrations (50 and 225 µg/ml) to provide additional safety information regarding the thyroid follicular epithelial degeneration that was observed in belimumab-treated monkeys.

No specific staining of the human tissues by the belimumab antibody was identified at any concentration. Two of the 34 cynomolgus tissues tested (exocrine pancreas and cervical epithelial cells) demonstrated binding of belimumab in tissue from one monkey. One monkey showed strong positive staining of zymogen granules of the pancreas at 2 and 10 µg/ml belimumab and a different monkey showed light staining of the basal layers of the cervical epithelium at 10 µg/ml belimumab, but not at 2 µg/mL. Additional sections of thyroid from two cynomolgus monkeys were stained with anti-BLyS antibody at concentrations of 50 and 225 µg/ml. No staining of the thyroid occurred.

The pancreatic staining was observed in tissue tested from only 1 of 4 animals and the cervical staining was observed in tissue tested from only 1 of 3 animals and in both tissues the involved organs looked normal histologically. There were no treatment related effects of belimumab identified in these tissues in the 4 -week or 6-month toxicology studies of belimumab in cynomolgus monkeys.

2.3.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment for belimumab has been submitted in the MAA dossier. As a monoclonal antibody belimumab is expected to be degraded like other proteins into small peptides and amino acids. Excretion of those will not pose an environmental risk. Furthermore, the excipients used in the formulation of belimumab do not pose a risk to the environment either. Therefore, specific ecotoxicity studies were not performed with belimumab. This is in line with the applicable guideline on environmental assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) and acceptable to CHMP.

2.3.6. Discussion on non-clinical aspects

BLyS has been shown to exist in both soluble and membrane bound forms. Experiments performed indicate that belimumab specifically recognizes only soluble BLyS. Belimumab was shown to be a neutralising monoclonal antibody as defined by its ability to disrupt BLyS-BLyS receptor interaction for all three BLyS receptors and thereby inhibit the murine splenocyte proliferation induced by both human and cynomolgus monkey BLyS.

The cynomolgus monkey was considered as the most relevant species in nonclinical studies since the monkey and human BLyS share 96.4% amino acid identity across the full length protein and 98% amino acid identity in the cleaved soluble portion of BLyS which constitutes the biological active form of the molecule. In addition, CD20+ B lymphocytes from cynomolgus monkey express BLyS receptors at levels comparable to those on human B lymphocytes. Furthermore, as with human samples, the tissue cross reactivity study showed no specific binding in monkey tissues considered related to belimumab. Overall, the preclinical data that support selection of the monkey as the most relevant species are considered satisfactory. The CHMP also considered the Applicant's approach for selecting a single relevant species for the toxicology studies adequately justified and supported by data.

Repeat-dose toxicity studies were performed for 4 weeks or 6 months, respectively. Aside from effects associated with the pharmacological activity of belimumab, there were few noteworthy findings in the toxicology studies indicating a low potential for toxicity. Most of the findings in the toxicity studies were reversible and could be related to the pharmacological effect of belimumab. The Applicant's justification for selection of 50 mg/kg as the high dose in the repeat dose toxicity studies was considered acceptable by CHMP. The pharmacokinetic profile of belimumab in the monkey is in agreement with the pharmacokinetic profile in humans.

With regard to the Applicant's justification for not conducting a carcinogenicity study with belimumab, CHMP recognized that a suitable animal model might be difficult to find due to its low tolerability in rodents. However, given that belimumab has a new immune modulatory mechanism of action (i.e., inhibition of BLyS-BLyS interaction), the Applicant was asked to further discuss the long-term suppressive effects on B-cells in relation to the risk for development of malignancies to allow a full risk assessment of potential carcinogenicity. In its response the Applicant discussed available literature data on the role of BLyS in malignancy, and concluded that these data do not suggest a risk for carcinogenicity. The Applicant further argued that the potential risk for malignancy with belimumab can only be evaluated in a clinical setting, which was endorsed by CHMP. The risk to develop cancer due to long-term modulation of the immune system is reflected in the RMP and a warning has been added in the SPC. Furthermore, a post-approval long-term safety study will be conducted that will assess the incidence of malignancies, among other safety concerns.

In reproductive studies in pregnant cynomolgus monkeys, belimumab treatment was not associated with direct or indirect harmful effects with respect to maternal toxicity, developmental toxicity, or teratogenicity. Treatment-related findings were limited to the expected reversible reduction of B cells

in both dams and infants and reversible reduction of IgM in infant monkeys. These findings are reflected in the SPC. While an overall higher incidence of fetal losses and infant deaths were observed in the combined treatment groups compared to the control, these findings were not considered appropriate for inclusion in the product information due to the insensitivity of the model as well as the high rate of spontaneous occurrences of these events.

Based on the data from nonclinical studies in the cynomolgus monkey, immunogenicity rates were considered low irrespective of the assay used to quantify the presence of anti-belimumab antibodies.

The tissue cross reactivity study indicated no specific binding of belimumab in any of the human tissues investigated. The pancreatic and the cervical staining seen in the monkey were not correlated to any histological changes and were not seen in in human tissues. The toxicity studies in monkeys did not show any findings related to these tissues. CHMP agreed with the applicant that unspecific tissue binding for belimumab seems low.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical program for belimumab was planned and executed in consideration of the need for long-term dosing in the target patient population and the fact that SLE often affects women of childbearing potential. The data provided is considered adequate and in line with the requirements of applicable guidelines for this type of products, particularly the ICH S6 Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95).

Intravenous and subcutaneous administration to monkeys resulted in the expected reduction in the number of peripheral and lymphoid tissue B cell counts with no associated toxicological findings. Beyond those finding which are related to the pharmacological action of belimumab, non-clinical data did not reveal any special hazard for humans based on studies of repeated dose toxicity and toxicity to reproduction.

Relevant information especially regarding the reproductive study findings and the effect of belimumab on male and female fertility are appropriately reflected in the SPC. Furthermore, the potential risk of malignancies has been included in the RMP and will be assessed in a clinical post-approval safety study.

2.4. Clinical aspects

2.4.1. Introduction

The biological activity of BLyS coupled with the knowledge that BLyS is upregulated in patients with SLE and other humoral autoimmune diseases highlighted the potential role for a BLyS antagonist in the treatment of SLE leading, in turn, to the development of belimumab.

Belimumab administered as an IV infusion in subjects with SLE has been studied in one Phase 1, one randomized Phase 2 as well as in two randomized, placebo-controlled Phase 3 studies. The long-term safety of belimumab is further evaluated in three open-label continuation trials. In addition, the applicant is conducting studies with belimumab in other therapeutic indications (e.g. rheumatoid arthritis) as well as evaluating a subcutaneous (SC) route of administration. An overview of the clinical development program is given in the table below.

Benlysta is indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g positive anti dsDNA and low complement) despite standard therapy.

The recommended dose regimen is 10 mg/kg of IV belimumab on Days 0, 14 and 28, and at 4 week intervals thereafter.

There are currently no EMA/CHMP scientific guidelines available for this indication. Scientific advice was received from the European Medicines Agency on clinical aspects of the development programme for belimumab.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Identifier	No. of Study Sites and Region	Study Start; Study Status & Date; Total /Target Enrollment	Study Objectives	Study Design	Diagnosis/ Key Inclusion Criteria	Treatment Details (Drug, Dose, Form, Route, Frequency, Duration)	No. of Subjects by Arm (completed)	Gender F/M, Mean Age (range) Race	Primary Endpoints
Randomized, Placebo-controlled Trials of Belimumab Administered IV in Subjects with SLE									
LBSL01 Module 5.3.3.2	16 US	Feb 2002 Completed Mar 2003 70/64-80	Safety and PK	DB, DE, MC, PC, R, (Phase 1)	SLE with stable disease activity for a period of at least 2 months prior to screening	Belimumab 1 mg/kg 4 mg/kg 10 mg/kg 20 mg/kg Placebo IV infusion: Single dose or 2 infusions 21 days apart.	57 (57) 15 (15) 14 (14) 14 (14) 14 (14) 13 (13)	64F/6M 40 (22-80Y) 50% White 47% Black 3% Other	Safety, Tolerability, Immunogenicity PK, PD
LBSL02 Module 5.3.3.2	59 58 US 1 Canada	Oct 2003 Completed Jun 2006 449/412	Safety and efficacy	DB, DR, MC, PC, PG, R (Phase 2)	Active SLE disease (SELENA SLEDAI disease activity score ≥ 4 at screening), stable SLE treatment regimen and history of measurable autoantibodies	DB, PC treatment period: Belimumab 1 mg/kg 4 mg/kg 10 mg/kg Placebo IV infusion on Days 0, 14, 28 and every 28 days thereafter for 48 weeks Optional 24-week extension period (all subjects received belimumab)	 114 (87) 111 (94) 111 (90) 113 (93) 345 (321)	419F/30 M 42 (20-75 Y) 70% White 24% Black 2% Asian 4% Other	Percent change in SELENA SLEDAI score at Wk 24 and Time to 1st flare over 52 wks

Study Identifier	No. of Study Sites and Region	Study Start; Study Status & Date; Total /Target Enrollment	Study Objectives	Study Design	Diagnosis/ Key Inclusion Criteria	Treatment Details (Drug, Dose, Form, Route, Frequency, Duration)	No. of Subjects by Arm (completed)	Gender F/M, Mean Age (range) Race	Primary Endpoints
HGS1006-C1056 (BLISS-76) Module 5.3.3.2	136 65 North America 62 EU 9 South America	Feb 2007 Completed Feb 2010 819/810	Safety and efficacy	DB, MC, PC, PG, R (Phase 3)	Active SLE disease (SELENA SLEDAI score ≥ 6) stable SLE treatment regimen, and positive ANA/anti-dsDNA	Belimumab 1 mg/kg 10 mg/kg Placebo IV infusion on Days 0, 14, 28 and then every 28 days thereafter for 72 wks	 271 (216) 273 (209) 275 (205)	764F/55M 40 (18-73 Y) 70% White 14% Black 3% Asian 13% Other	Response at Week 52 (defined in Section: ≥4 pt reduction from baseline in SELENA SLEDAI score and no worsening in PGA and no new BILAG 1A/2B
HGS1006-C1057 (BLISS-52) Module 5.3.3.2	92 41 Asia Pacific 40 Latin America 11 EU	May 2007 Completed May 2009 865/810	Safety and efficacy	DB, PC, PG, R (Phase 3)	Active SLE disease (SELENA SLEDAI score ≥ 6), stable SLE treatment regimen, positive ANA/anti dsDNA	Belimumab 1 mg/kg 10 mg/kg Placebo IV infusion IV infusion on Days 0, 14, 28 and then every 28 days thereafter for 48 wks	 288 (240) 290 (241) 287 (226)	821F/44M 36 (18-71 Y) 38% Asian 27% White 4% Black 33% Other	Response at Week 52: ≥4 pt reduction from baseline in SELENA SLEDAI score and no worsening in PGA and no new BILAG 1A/2B
Long-term Continuation Trials in Subjects with SLE									
LBSL99 Module 5.3.5.2	58 57 US, 1 Canada	May 2005 Ongoing 321 eligible/ 296 enrolled	Safety and efficacy	MC, NR, OL, UC (Phase 2)	Subjects who completed the LBSL02 trial and achieved a satisfactory response	Belimumab 10 mg/kg IV infusion once every 28 days	296	276F/20M 43 (20-75 Y) 72% White 22% Black 2% Asian 5% Other	Long term safety
HGS1006-C1066 Module 5.3.5.4	52 US	May 2008 Ongoing 233[2]/428[1] (max)	Safety, efficacy, biomarkers, organ damage	R, UC (Phase 3)	Continuation study for US subjects who completed C1056	Belimumab 1 or 10 mg/kg[3] IV infusion once every 28 days	Not available at this time	Not available at this time	Long term safety Organ damage (SLICC/ACR Damage Index)

Study Identifier	No. of Study Sites and Region	Study Start; Study Status & Date; Total /Target Enrollment	Study Objectives	Study Design	Diagnosis/ Key Inclusion Criteria	Treatment Details (Drug, Dose, Form, Route, Frequency, Duration)	No. of Subjects by Arm (completed)	Gender F/M, Mean Age (range) Race	Primary Endpoints
HGS1006-C1074 Module 5.3.5.4	112 2 North America 43 EU 36 South America 31 Asia Pacific	Apr 2008 Ongoing 712[2]/1265[1] (max)	Safety and organ damage	R, UC (Phase 3)	Continuation study for subjects outside US who completed C1056 or C1057	Belimumab 1 or 10 mg/kg[3] IV infusion once every 28 days	Not available at this time	Not available at this time	Long term Safety Organ damage (SLICC/ACR Damage Index)

2.4.2. Pharmacokinetics

Belimumab is a human IgG1λ monoclonal antibody specific for soluble human BLyS. Due to the nature of the molecule, traditional pharmacokinetic studies exploring the absorption, distribution, metabolism and elimination (ADME) have not been performed, but rather has the systemic exposure in patients been described.

The pharmacokinetic documentation included data from healthy volunteers (study C1058, SC administration) as well as patients with SLE (Phase 1 study LBSL01; Phase 2 study LBSL02; Phase 3 studies C1056 and C1057). The data obtained in SLE patients have been combined in a joint population PK analyses which, according to the Applicant, formed the basis for the definitive assessment of the PK profile of belimumab.

Analytical methods

Two methods have been used for quantifying belimumab in human serum from clinical studies. An ELISA method was used for the Phase 1 and 2 studies, while an ECL-based assay was used to detect belimumab in serum samples from both Phase 3 studies. Subsequent to use in Phase 3 studies, the specifications for the control and standard curve samples in the ECL assay were modified and the modified assay was shown to be comparable to the previous version of the assay. The range of interpolation following dilution was 0.277-20 ng/mL and 0.25-120 ng/mL for the ELISA and ECL method, respectively. The methods have been sufficiently documented and demonstrate adequate accuracy and precision.

PK in healthy subjects

Study C1058 is a randomized, parallel-group, open-label, phase I, single-dose study of belimumab in healthy subjects. The study was designed to evaluate the absolute bioavailability and safety of a single SC dose (100 mg) of belimumab in healthy subjects.

A total of 36 healthy subjects, 18 to 63 years of age, were enrolled and randomized to two treatment groups. In the IV group, subjects received a single IV dose (100 mg) of belimumab as a 1-hour infusion. In the SC group, subjects received a single 100 mg dose of belimumab by SC injection into the abdomen or thigh. Intensive blood samples were collected in both groups within 70 days following drug administration. Belimumab PK parameters were calculated using non-compartmental methods.

After SC administration, the absolute bioavailability of belimumab was 67.23% (95% CI: 56.51% to 77.95%), T_{max} was 5.0 days. Mean C_{max} and AUC (0-∞) were 10.63 µg/mL and 284.8 day*µg/mL, respectively. After IV administration, mean C_{max} and AUC (0-∞) were 36.67 µg/mL and 413.3 day*µg/mL, respectively. Mean elimination half-life was 12.6 days after SC administration and 13.5 days after IV administration.

PK in target population

Study LBSL01 is a Phase 1, multi-center, randomized, double-blind, placebo-controlled, dose-escalation study of belimumab in subjects with SLE. Belimumab dose levels of 1, 4, 10, and 20 mg/kg were administered IV as a single dose (Cohorts 1-4) or double dose (2 doses, 21 days apart; Cohort 5-8). Belimumab or placebo was administered by IV infusion over a period of approximately 2 hours

In study LBSL01 serum belimumab concentrations were measured following an extensive sampling schedule after dosing and the data were analysed by compartmental methods. A 2-compartment infusion model was used to evaluate serum belimumab concentration-time data from all eight cohorts. Various weighting schemes were evaluated.

There were no significant differences in PK parameters between single and double dose cohorts. Overall, belimumab PK are linear across the 1 to 20 mg/kg dose range in this study. For the two subjects with positive anti-belimumab antibody responses, the observed serum concentrations were 2 to 3.5-fold lower than the predicted values at the time points.

However, the results obtained from study LBSL01 may not be entirely predictive of belimumab PK after chronic administration as belimumab was administered only short term (single or double dose) in this study.

The serum belimumab concentration data obtained from the Phase 2 (study LBSL02) and Phase 3 (C1056 and C1057) long-term dosing trials employed sparse sample collection and were used in the

population PK analysis (for further study details see section on Clinical efficacy below). In these studies the concentration data were summarized using mean, median, standard error, standard deviation, %CV, geometric mean, 95% confidence interval, and number of subjects (N). The exposure linearity was evaluated using power relationship ($y = Ax^B$) and linear regression of the logarithmically transformed dose versus logarithmically transformed pharmacokinetic variables.

Population PK analysis

The population PK (PopPK) analysis served to complement the non-compartmental analysis (NCA) of belimumab PK by providing assessments of dose linearity and effect of covariates on the drug PK.

Data from intravenous dosing studies in SLE patients (one Phase 1 study (LBSL01, N=57), one Phase 2 study (LBSL02, N=424) and two Phase 3 studies (C1056, N=544; 1057, N=578) with a total of 1,603 subjects were included in the data set underlying the PopPK analysis. A non-linear mixed-effects model describing the pharmacokinetics of belimumab was developed using NONMEM 6.2 using the FOCE-I estimation method. The objectives of this study were to develop a population pharmacokinetic model that characterizes the disposition of belimumab following intravenous administration to subjects with SLE and to evaluate the potential effect of selected subject covariates on key pharmacokinetic parameters. In addition, the PopPK model allows estimating individual subject PK parameters in efficacy trials for potential exposure-response analysis.

The pharmacokinetics of belimumab was well described by a linear 2-compartment model with clearance from the central compartment. The model included several covariate effects (9 covariate effects related to patient characteristics, 2 covariate effects related to co-medications and 5 covariates related to study and dose effects.) whereof only the effect of body size was considered clinically relevant.

Absorption and bioavailability

Belimumab is administered as an intravenous (IV) infusion and bioavailability is complete. Maximum serum concentrations of belimumab were generally observed at, or shortly after, the end of the infusion. The maximum serum concentration following the 10 mg/kg dose in the phase 3 studies was estimated to 313 µg/ml (range: 173-573 µg/ml) based on empirical Bayes individual pharmacokinetic parameters using the population pharmacokinetic model.

Distribution and elimination

Following single IV administration, serum belimumab concentrations decline in a bi-exponential manner consistent with a 2-compartment model with first order elimination from the central compartment. The mean volume of distribution at steady-state (V_{SS}) was 5.29 L in the targeted Phase 3 population with 10 mg/kg dosing. The small V_{SS} value indicates that belimumab is confined primarily to the extracellular fluid volume consistent which is typical for the class of IgG1 monoclonal antibodies. The estimated population terminal half-life of 19.4 days (for 10 mg/kg dosing) and clearance of 215 mL/day (corresponding to 3.2 mL/day/kg) in the targeted Phase 3 population with 10 mg/kg dosing are consistent with results from other IgG_1 monoclonal antibodies. NCA and PopPK showed fairly similar results.

In the population PK analysis the central (V1) and peripheral volumes of distribution (V2) were estimated to 2,560 and 2,730 mL, respectively (corresponding to 38.6 mL/kg and 41.2 mL/kg). Between-subject variability in total systemic clearance (CL), central volume of distribution (V1) and

peripheral volume of distribution (V2) was modest with coefficients of variation being estimated at 26.4% for CL, 19.9% for V1, 31.1% for V2.

IgG monoclonal antibodies are in general eliminated via non-specific endocytosis followed by proteolysis and/or by receptor-mediated endocytosis and catabolism. Thus, the general studies concerning excretion and metabolism have not been performed, which was acceptable to CHMP.

Immunogenicity

The effect of antibodies toward belimumab (ADA) on the systemic exposure was explored in all clinical trials and in the population PK analysis. The methodologies employed for measuring anti-belimumab antibodies changed over time. The assay to evaluate the presence of neutralising anti-belimumab antibody in a serum sample was performed using fluorometric immunoassay methods. Only samples determined to be positive for anti-belimumab antibody (by either or both of the immunogenicity screening assay formats) were to be analyzed in the neutralisation assay.

Immunogenicity was observed relatively infrequently. In the two Phase 3 studies, 73 out of 559 subjects in the 1 mg/kg group and 5 out of 563 subjects in the 10 mg/kg group tested positive for anti-belimumab antibodies at, at least one time point (i.e. both persistent and transiently positive).

Assay sensitivity for neutralising antibodies and non-specific anti drug antibody (ADA) is limited by the presence of active drug in the collected samples. The true occurrence of neutralising antibodies and non specific anti drug antibody in the study population is therefore not known.

Dose proportionality and time dependencies

The variability in AUC ranged from 21%CV to 42%CV. The systemic exposure appears to be independent of dose and time over the studied doses (1-20 mg/kg) and duration (up to 1 year).

In the PopPK model, while the covariate effect of dose group on V2 in the final model indicates that exposure is not perfectly dose-linear, the impact of this effect on steady-state exposure is relatively minor. Moreover, graphical data analysis and testing baseline antibody target (BLyS) levels as a covariate effect on CL did not reveal evidence of clinically significant CL mediated by binding of belimumab to its target. It was concluded that target-mediated disposition (TMD) does not appear to play a substantial role in belimumab pharmacokinetics and that belimumab pharmacokinetics are approximately dose proportional for the tested dosing regimens.

The results of the PopPK analysis indicated that the belimumab PK parameters were time invariant over the period for which the PK data were available (induction period up to approx. 12 weeks following the first dose). The effect of time on CL seems to be not significant, and there was no trend in the conditional weighted residuals versus time, indicating that the PopPK parameters are time-invariant.

Special populations

No specific studies have been performed with respect to special populations, but information is obtained from the clinical studies and the population PK analysis. The lack of such studies in impaired organ function is acceptable given that this is a monoclonal antibody for which elimination via renal excretion, biliary excretion or hepatic metabolism is limited. With respect to renal function, the population PK model predicts clearance to change by -36% and 9% for a subject with creatinine clearance of 10 and 120 ml/min, respectively, compared with a subject with creatinine clearance of

80 ml/min. In addition, clearance was predicted to increase by 14% with proteinuria (>2 g/24h). However, neither of these effects was considered to have a clinically significant effect on belimumab clearance. Subsequently, no dose adjustments are proposed in either renal or hepatic impairment, which in general is accepted. However, due to the lack of available data, caution is recommended in patients with severe renal impairment.

Both clearance and volume of distribution increase with increasing body weight. An additional effect of BMI on volume of distribution was identified implying that a subject with a higher BMI but otherwise weight-matched will have a lower volume of distribution, and accordingly a higher maximum plasma concentration. Taken together, the body size effects do not predict that the systemic exposure will increase directly in proportion to dose, and given the body weight adjusted dosing, underweight subjects will experience lower systemic exposure compared with the typical subjects and the opposite will be true for obese patients. A review of efficacy aspects did not indicate decreased efficacy in underweight patients although the data are limited. With respect to safety, similar adverse event patterns were observed for obese subjects apart from gastrointestinal AEs. Higher rates of nausea, vomiting and diarrhoea were observed in obese patients; however, none of these events were serious and no dose adjustment is recommended for either underweight or obese patients. This is reflected in the SPC.

Concerning gender the popPK analysis did not identify an effect but cannot be considered conclusive due to the fact that the main part of the patients were female. An effect is, however, not expected after body weight adjustment.

Furthermore, no effect of race on the pharmacokinetics of belimumab has been observed; also, no effect of age has been identified, but the analysis is only conclusive up to 65 years of age due to limited data above 65 years. Information in children and adolescents is currently not available. The absence of paediatric data is included as important missing information in the RMA and a study in children aged 5-17 years will be conducted.

Pharmacokinetic interaction studies

No formal drug-drug interaction study was carried out by the Applicant because belimumab is a protein and does not undergo metabolism by the cytochrome P450 enzymes. Concomitant medications were explored in the population PK analysis but concomitant medications were in some cases grouped according to therapeutic area and there is no information of the dose levels used and whether the patients actually received the drug at the time of sampling. Thus, the results cannot be used as firm evidence of the size of an interaction or the lack of interaction, but merely as a general observation/support that no large/major interaction was observed, and cannot be used as the basis for a statement in the SmPC.

Pharmacokinetics using human biomaterials

As a monoclonal antibody, belimumab is not metabolized by the cytochrome P450 system; instead, it is cleared through cellular catabolism following nonspecific uptake by pinocytosis. Accordingly, no in vitro studies using human biomaterials, such as drug-drug interaction studies, were conducted. This was acceptable for CHMP.

2.4.3. Pharmacodynamics

Belimumab is a molecule expected to reduce B-cell counts by blocking the B-cell survival factor, BLyS. An agent that reduces B-cell counts might also be expected to reduce the products of B cells (i.e., serum immunoglobulins, including autoantibodies). A reduction in autoantibodies, in turn, could be expected to be associated with increases in complement levels, which are known to be reduced in SLE subjects with active disease, partly as a result of autoantibody fixation of complement that results in organ damage.

Thus, pharmacodynamic endpoints that have been evaluated in all clinical studies of IV belimumab include serum immunoglobulin levels, autoantibody levels, serum complement (C3 and C4) levels, and B-cell counts. As these are endpoints in clinical studies that support the safety and efficacy evaluation of belimumab, only a summary of results from the Phase 1 studies are provided here; more detailed descriptions of these pharmacodynamic endpoints can be found in the summaries of the individual clinical Phase 2 and 3 studies.

Autoantibodies that have been assessed in clinical studies include anti-dsDNA, anti-nuclear antibodies (ANA), anti-Smith antibodies (anti-Sm), anti-RNP, aCL, anti-SS-A (anti-Ro), anti-SS-B (anti-La), and anti-ribosomal P. The only autoantibody discussed in detail in this section is the anti-dsDNA marker, as it is present at baseline in the greatest number of subjects (~70% of subjects across the Phase 2 and Phase 3 studies in SLE).

Mechanism of action

Belimumab inhibits the biological activity of BLyS. The primary function of BLyS is the promotion of B-lymphocyte survival and differentiation. In humans, soluble BLyS is biologically active and produced primarily by monocytes and activated neutrophils. The biological effect of BLyS is predominantly mediated through the BR3 receptor. The immediate downstream effects of BLyS signalling are on intracellular molecules that regulate apoptosis/cell survival. BLyS signalling through its main receptor BR3 is generally acknowledged to result in an anti-apoptotic program that is mediated by cooperative activation of the classical and alternative NF-κB pathways. For details of the belimumab mode of action see also section on Non-clinical aspects.

Ex vivo studies with serum and synovial fluid from autoimmune patients, primarily SLE and RA, have demonstrated that BLyS levels in autoimmune patient populations are significantly higher than those observed in normal healthy controls. Elevated BLyS levels have been found to be positively correlated with elevated anti-dsDNA, IgG, and disease activity and prospectively collected data from patients with SLE showed an association between an elevated BLyS level and a subsequent increase in disease activity.

Primary and Secondary pharmacology

The applicant conducted two Phase 1 studies in which the effect of a single or double doses of belimumab on immunoglobulin levels and B cells was assessed (LBSL01 in SLE subjects and C1058 in healthy volunteers).

Phase I clinical trials

In the Phase 1 study LBSL01, measurements of serum immunoglobulins (IgG, IgM, IgA, IgE), anti-dsDNA antibodies, complement and B cells were assessed on Day 0 prior to dosing, and generally at 2-4 week intervals following dosing through a 12 week wash-out period. In general, the percent decrease in serum immunoglobulins appeared to be greater for belimumab treatment groups relative to placebo in LBSL01. No treatment effect on anti-dsDNA levels were observed in the complete study population.

No consistent effect on complement levels was noted in LBLS01. A treatment effect for reductions in CD20+ cells relative to placebo was only observed in a subset of subjects with higher baseline CD20+ B-cell counts observed in the belimumab-treated subjects overall. Reductions in plasmacytoid (CD20+/CD138+) cells in belimumab-treated were observed only at isolated timepoints.

In study C1058 (healthy volunteers, SC administration) measurements of serum immunoglobulins (IgG, IgM, IgA) and B cells were assessed on Day 0 prior to dosing, and at 4 timepoints within the 70-day wash-out period. Mean percent reductions in IgG, IgA, and IgM relative to baseline were observed from Day 28 onward in both the IV and SC treatment groups, but values in all cases were within 10% of mean baseline values. No consistent effects on activated B cells and plasma cells were observed in C1058. However, mean and median CD20+/CD27+ memory B cell counts were increased relative to baseline at all post-treatment visits in both the IV and SC treatment groups, which is similar to effects seen on B cells in the repeat dose Phase 2 and Phase 3 studies

2.4.4. Discussion and conclusion on clinical pharmacology

Belimumab is a recombinant, human, IgG1λ monoclonal antibody that binds to and inhibits the biological activity of BLyS. Belimumab binds soluble BLyS with high affinity and blocks the interaction of BLyS with its three receptors resulting in the inhibition of the downstream effects of BLyS *in vitro* and *in vivo*. Belimumab does not recognize membrane-bound BLyS.

The human pharmacokinetic properties of belimumab been characterised sufficiently in SLE patients and are in line with those observed for other IgG monoclonal antibodies. The PK profile was shown to be linear across the 1 to 10 mg/kg dose range. The estimated population terminal half-life of 19.4 days is consistent with results from other IgG1 monoclonal antibodies.

At the administered doses there are no indications of dose or time dependency. The effects of body size (BW on central CL and BW or BMI on V1) had the strongest impact on belimumab PK parameters. These effects are addressed by weight normalized dosing. Other patient characteristics had small to moderate effects and did not warrant dose adjustments, particularly, given the safety results which indicate that belimumab has a safety profile comparable to placebo, with no suggestion of a dose-response relationship for adverse events.

The lack of excretion data is acceptable given that the main elimination of belimumab does not occur via biliary or renal excretion. No data has been submitted regarding the metabolism of belimumab. This was considered acceptable by CHMP given that the main elimination of belimumab does not occur via metabolism catalysed by enzymes normally involved in drug metabolism.

The assays sensitivity for neutralizing antibodies and non-specific anti-drug antibody (ADA) are limited by the presence of active drug in the collected samples. Therefore, there is very limited insight in the true occurrence of neutralizing antibodies and non-specific anti-drug antibody in the study population and no definitive conclusions can be drawn regarding the effects of immunogenicity on belimumab PK. Information on the immunogenic potential for belimumab has been added to the SPC. Furthermore, the Applicant will continue to assess the incidence of formation of anti-belimumab antibodies using an ECL-based bridging assay in ongoing and future clinical studies.

It is not fully known how soluble BLyS is related to the pathophysiology of SLE and to what degree the binding of soluble BLyS affects the course or the severity of SLE. The controlled studies in subjects with SLE did not show a relationship to belimumab dose with respect to decreases in immunoglobulin levels or normalization of anti-dsDNA. For other assessments, a dose trend was observed, such as for

complement levels, conversion from seropositive to seronegative for anti-Sm and anti-ribosomal P antibodies, and reduction in plasma cells.

2.5. Clinical efficacy

The objectives of the clinical development program for belimumab were to demonstrate the efficacy, safety, and impact on quality of life of belimumab in combination with standard of care therapy in the treatment of patients with SLE.

The efficacy studies from the belimumab clinical development program in SLE include LBSL02, C1056 and C1057. The efficacy data from the Phase 2 (LBSL02) study are considered supportive and hypothesis generating, while the Phase 3 trials are considered pivotal and hypothesis confirming.

2.5.1. Dose response study

In the Phase 2 study (LBSL02) the efficacy of three doses (1, 4 and 10 mg/kg) of belimumab in combination with standard care was evaluated as compared to placebo (plus standard care) in study subjects with active SLE.

Eligible subjects had a clinical diagnosis of SLE according to the ACR criteria and "active" SLE disease, defined as a SELENA SLEDAI disease activity score of at least 4 at screening and a history of measurable autoantibodies; a positive autoantibody result was not required at screening.

The two co-primary efficacy endpoints were percent change in SELENA SLEDAI at week 24 and time to first SLE flare (using the SELENA SLEDAI flare index) over 52 weeks. Analyses were performed on the modified intent-to-treat (mITT) population, defined as the subset of all randomized subjects who received at least 1 dose of study agent.

Results in LBSL02

Belimumab was administered to 336 subjects, while 113 subjects received placebo (total 449). A total of 364 subjects completed the 52-week treatment period of the study, 345 of whom received treatment in the optional 24-week extension period. Of the 321 subjects completing the extension period, 296 were enrolled and treated in the LBSL99 study. Overall, the dropout rate in the initial 52-week treatment period was 19% (85/449), with no apparent difference among treatment groups. The most frequent reasons for withdrawal from the study were subject request and lack of compliance (5.3% each) in the placebo arm and subject request (7.4%) followed by AE (6.0%) in all active groups combined.

Over 93% of the subjects in LBSL02 were female, with a mean age of 42 years and being the majority of subjects < 45 years of age. Approximately 70% of the population was white, 24% (n = 106) was black and Hispanic/Latino ethnicity made up 19% of the population. In general, key baseline demographics were balanced across treatment groups.

Superior efficacy in the co-primary endpoint, percent change in SELENA SLEDAI score at Week 24, was not achieved. The mean percent decrease in SELENA SLEDAI score was numerically better than placebo for the 1 and 10 mg/kg groups with an average of approximately 23% each compared with 17% in the placebo group, while the 4 mg/kg group had a mean percent decrease of 11%. These trends continued through Week 52/56. Furthermore, belimumab did not show benefit as measured by the pre-specified major secondary endpoints of SELENA SLEDAI, including AUC of SELENA SLEDAI score and percent change of SELENA SLEDAI at Week 52.

Table 7-1 Percent change from baseline in SELENA SLEDAI score at Week 24 (MITT with LOCF)

SELENA SLEDAI Score (Mean ± SE)	Placebo N = 113	1.0 mg/kg N = 114	4.0 mg/kg N = 111	10.0 mg/kg N = 111	All Active N = 336
n	113	114	111	111	336
Baseline	9.5 ± 0.50	9.9 ± 0.44	9.4 ± 0.45	9.5 ± 0.39	9.6 ± 0.25
Absolute Change at Week 24	-2.2 ± 0.49	-2.6 ± 0.41	-1.9 ± 0.42	-2.6 ± 0.44	-2.4 ± 0.24
Percent change at Week 24	-17.2 ± 5.10	-23.3 ± 4.43	-11.3 ± 5.40	-23.7 ± 4.22	-19.5 ± 2.73
Mean difference from placebo	-	-6.10	5.94	-6.48	-2.25
95% CI for mean difference	-	(-19.4, 7.2)	(-8.7, 20.6)	(-19.6, 6.6)	(-13.2, 8.7)
P value from t-test[1]	-	0.3677	0.4244	0.3296	0.6863

[1] P value for pairwise comparison between each active treatment and placebo group.

The study also failed to demonstrate differences in Time to first mild/moderate or severe SLE flare (SFI) over 52 weeks (67 days for belimumab combined vs. 83 days for placebo), which were the co-primary endpoints of the study. The number of flares was high and the majority (86% or more) of both belimumab and placebo subjects flared by Week 52, mostly in the initial 24weeks.

In *post hoc* analyses, a belimumab treatment effect was observed for decreases in SELENA SLEDAI score from baseline to Week 52 in subjects with the following baseline characteristics: anti-dsDNA antibody positivity, low C3, low C4, and prednisone dose >7.5 mg/day at baseline (pre-specified subgroup). There were favorable trends in SELENA SLEDAI scores observed in the subgroup of subjects with baseline SELENA SLEDAI scores ≥8 (pre-specified subgroup) and ANA ≥1:80 at both screening and Day 0.

The results of the Phase 2 study guided the selection of a patient population (autoantibody positive, SELENA SLEDAI score ≥ 6) that was most likely to benefit from belimumab treatment. Furthermore, dose selection (1 and 10 mg/kg) as well as selection of the composite endpoint (SRI at Week 52) as the primary efficacy endpoint in the Phase 3 trials were derived from the Phase 2 data.

2.5.2. Main studies

Two Phase 3 trials have been conducted in patients with SLE and are considered as pivotal support for this MAA. The two Phase 3 trials were multicenter, randomized, double-blind, placebo controlled trials with similar study design which considered the post-hoc subgroup findings of the Phase 2 study (LBSL02). Placebo-controlled treatment was continued through week 52 in study C1057 (BLISS-52) and through Week 76 in study C1056 (BLISS-76), respectively.

The study characteristics described below apply to both Phase 3 studies unless indicated differently.

Methods

Study Participants

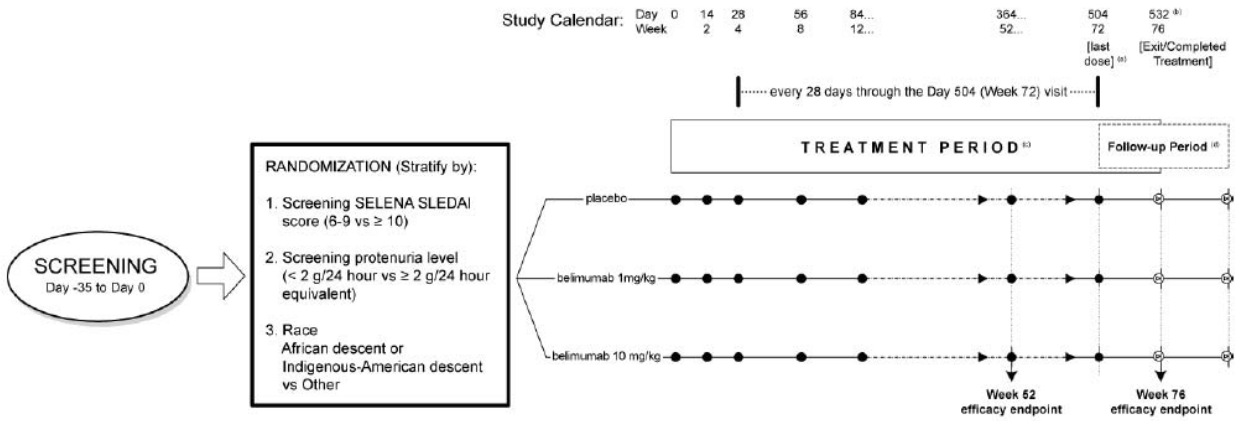
Eligible subjects should have a clinical diagnosis of SLE according to the ACR criteria, have an active SLE disease defined as a SELENA SLEDAI score ≥6 at screening and should be positive for autoantibodies, defined as ANA (titer ≥1:80) and/or anti-dsDNA (≥30 IU/mL) at two time points prior to randomization reflecting a more active disease than the Phase 2 study.

The selection criteria for the Phase 3 program were discussed and agreed with EMA in a formal scientific advice procedure prior to initiation of the Phase 3 trials, and are considered adequate. The

main exclusion criteria were active lupus nephritis or CNS disease requiring intervention, unstable or uncontrolled acute or chronic medical conditions. Further exclusion criteria were pregnancy, receipt of any B cell-target therapy at any time, receipt of an investigational agent within 60 days prior to Day 0 for non-biologics and within 1 year for biologics, IV cyclophosphamide (within 6 months), anti-TNF therapy, anakinra, IV immunoglobulin (IVIG), prednisone >100 mg/day, or plasmapheresis within 3 months or live vaccine within 1 month.

Treatments

Eligible subjects were randomized to one of three treatment groups: belimumab 1 mg/kg, belimumab 10 mg/kg, or placebo administered IV on Days 0, 14, and 28, then every 28 days through 52/76 weeks in addition to stable standard therapy.



[a] The last dose of study agent is given on the Day 504 (Week 72) visit to subjects NOT participating in the continuation protocol.
[b] Subjects continuing in the continuation protocol are dosed on the Day 532 (Week 76) visit. This Day 532 (Week 76) represents the 1st dose (ie, Day 0) of the continuation protocol. For subjects not participating in the continuation protocol, the Day 532 (Week 76) visit serves as the exit visit.
[c] The treatment period includes 72 weeks of study agent administration (Day 0 to the Day 504 visit) **and** a follow-up visit at Week 76 which is 4 weeks after the last dose of the study agent.
[d] The follow-up period includes 2 scheduled visits of 4 and 8 weeks after the last dose of study agent (Day 504/Week 72) for subjects not participating in the continuation protocol.

HGS# 000-6486

Figure 5-1 General study schema

Stable standard therapy consisted of the following (alone or in combination): prednisone or equivalent, anti-malarials, NSAIDs, or any immunosuppressive therapy (i.e. methotrexate, azathioprine, leflunomide, mycophenolate, calcineurin inhibitors, sirolimus, oral cyclophosphamide, 6 mercaptopurine, or thalidomide). Subjects who required changes in background SLE medications beyond that permitted by protocol were declared treatment failures/non-responders.

Concomitant therapy were restricted regarding anti-malarials, steroids, other immunosuppressive or immunomodulatory agents, HMG CoA reductase inhibitors, angiotensin pathway antihypertensives, NSAIDS and Aspirin.

Prohibited medication at any time during the study included other investigational agents (biologic or non-biologic), anti-TNF therapy (e.g. adalimumab, etanercept, infliximab), other biologics (e.g. rituximab, abatacept, interleukin-1 receptor antagonist [anakinra]), intravenous immunoglobulin (IVIG), IV cyclophosphamide, plasmapheresis.

Objectives

The objective of the Phase 3 studies was to demonstrate the efficacy and safety profile of belimumab in subjects with SLE as add-on to standard of care (SOC) therapy, including corticosteroids. In addition, the impact of belimumab on quality of life in subjects with SLE was to be evaluated.

While corticosteroid tapering was not an objective, a comprehensive use control was established and physicians were recommended to reduce CS doses provided that the patients remained stable at least 4 weeks.

Outcomes/endpoints

Primary efficacy endpoint

The SLE responder index (SRI), which evaluated response rate at Week 52, was used as the primary efficacy endpoint. The SRI is a composite endpoint resulting from the combination of three validated tools for estimating SLE disease activity: the SELENA SLEDAI, PGA and BILAG.

Response in SLE responder index (SRI) at Week 52 was defined as:

- ≥ 4 point reduction from baseline in SELENA SLEDAI score,

AND

- No worsening (increase of < 0.30 points from baseline) in PGA,

AND

- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (i.e. at Week 52).

This composite endpoint had been agreed in a scientific advice procedure. The individual components are described in more detail below.

SELENA SLEDAI score:

The SLEDAI is an index for assessing SLE disease activity (Bombardier et al, 1992). It captures a subject's condition over the 10 days prior to the visit. It is a weighted index in which signs and symptoms, laboratory tests, and physician's assessment for each of nine organ systems are given a weighted score and summed up if present at the time of the visit or in the preceding 10 days:

- Score of 8 each for CNS and vascular items
- Score of 4 each for renal and musculoskeletal items
- Score of 2 each for serosal, dermal, and immunologic items
- Score of 1 each for constitutional and hematologic items

The SELENA SLEDAI used in this study is a slightly modified version of the SLEDAI developed for a National Institutes of Health-sponsored multicenter study of estrogen/progesterone hormone use in women with SLE (Buyon et al, 2005; Petri et al, 2005). The maximum theoretical score for the SELENA SLEDAI is 105 (all 24 descriptors present simultaneously) with 0 indicating inactive disease. SELENA SLEDAI was assessed at screening and prior to dosing at Day 0, at Week 4, and at every scheduled study visit thereafter through Week 76/Exit except Weeks 56 and 64.

According to the Applicant classification of increased disease activity using the SELENA SLEDAI score has been described as an increase of 3 points or more (Petri, 1991a; Petri, 1999), and a reduction of

more than 3 points in SELENA SLEDAI score has been defined as an improvement (Gladman, 2000). Consequently, a reduction ≥4 was considered evidence of improvement.

PGA (Physician's Global assessment):

The PGA is a 0-10 cm visual analogue scale (VAS), anchored at 0 (none) and 3 (severe), with intermediate lines at 1 (mild), and 2 (moderate) designed for the physician to indicate the subject's overall disease activity at a particular visit (Petri et al, 1999).

PGA was assessed at screening, prior to dosing at Day 0, at Week 4, and at every scheduled study visit thereafter through Week 76/Exit except Weeks 56 and 64.

BILAG

The BILAG (British Isles Lupus Assessment Group) index is a clinical measure of lupus disease activity. BILAG scores patients based on the need for alterations or intensifications of therapy. The main distinguishing feature of the BILAG index from other disease activity indices is that disease activity in different organs/systems is reported separately.

Eight organ systems are being evaluated: general, mucocutaneous, neurological, musculoskeletal, cardiorespiratory, vasculitis, renal, and haematological. A score is calculated for each system depending on the SLE clinical manifestations (or signs and symptoms) present and whether they are new, worse, the same, improving, or not present in the last 4 weeks compared with the previous 4 weeks.

- **BILAG A**: The SLE disease manifestations considered severe in each system are those that would normally require high dose steroids (prednisolone >20 mg/day or equivalent) and/or cytotoxic agents; these define a BILAG A score.
- **BILAG B**: More moderate SLE disease manifestations that would be considered appropriate to treat with lower dose steroids, antimalarial drugs or NSAIDs contribute to a BILAG B score.
- **BILAG C**: Mild symptomatic SLE features that require only symptomatic therapy (e.g. analgesics and NSAIDs) contribute to a C score.
- **BILAG D**: If there are no current symptoms, but the system has previously been involved, then a D is recorded.
- **BILAG E**: If the system has never been involved an E score is assigned.

A BILAG flare is a worsening in one or more organ systems to an A score (from a B-E score) or a worsening in two or more organ systems to a B score (from a C-E score).

A BILAG response is defined as a BILAG A organ domain score that improves to B, C, or D or a BILAG B organ domain score that improves to C or D wherein the subject also has no moderate to severe worsening in another organ domain as defined by the subject's having a new BILAG A organ domain or two new BILAG B organ domain scores compared with baseline at the time of assessment.

The BILAG was assessed at screening, prior to dosing at Day 0, at Week 4, and at every scheduled study visit thereafter through Week 76/Exit except Weeks 56 and 64.

Secondary efficacy endpoint

Numerous secondary endpoints were included in the study protocols and analytical plans. The following were selected by the applicant as major secondary endpoints:

Table Major secondary endpoints in the Phase 3 trials

	Phase 2	Phase 3	
Efficacy Endpoints	**LBSL02**	**C1056**	**C1057**
Response rate at Week 76 (SELENA SLEDAI ≥ 4 point reduction and no worsening as measured by PGA and BILAG)	na	MS	na
% of subjects with ≥4 point reduction in SELENA SLEDAI at Week 52	ph[1]	MS	MS
Mean change in PGA at Week 24	os	MS	MS
% Subjects with prednisone (equivalent) reduction ≥ 25% from baseline to ≤7.5 mg/day during Weeks 40 – 52 (in subjects whose prednisone equivalent dose was > 7.5 mg/day at baseline)	na[2]	MS	MS
Mean change in SF-36 PCS at Week 24	os	MS	MS

MS = major secondary endpoint; na = not applicable; os = other secondary endpoint; ph = post-hoc.
[1] Performed post-hoc with drop-out = failure analysis, but without the concomitant medication failure rules.
[2] Similar major secondary endpoint in LBSL02, but threshold was ≥ 50% reduction from baseline.

Sample size

Approximately 810 subjects were to be randomized and treated in each of the two Phase 3 trials, with a target of at least 270 subjects per treatment group. This sample size was to provide at least 90% power at a 5% level of significance to detect a minimum of a 14% absolute improvement in the response rate for the 10 mg/kg belimumab group (or both 1 mg/kg and 10 mg/kg belimumab groups) relative to the placebo group at Week 52.

The sample size calculation used the most conservative estimate for the standard deviation (SD) in the population (i.e. population SD=50%) yielding an assumption of a 43% placebo response rate vs 57% belimumab response rate, with an average (population) response rate of 50% under the null hypothesis (i.e. active=placebo).

Randomisation

Subjects enrolled in the Phase 3 trials were randomized in a 1:1:1 ratio to one of the three treatment groups (1 mg/kg or 10 mg/kg belimumab or placebo), stratified by their screening SELENA SLEDAI score (6-9 vs ≥10), screening proteinuria level (<2 g/24 hour vs ≥2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs other, i.e. white European ancestors and Asian).

Blinding (masking)

Subjects were randomized once they had undergone all screening procedures and had been determined to be eligible for study participation.

Belimumab study drug was supplied as open-label vials and 3rd party unblinding was employed. The study agent was reconstituted and diluted by the unblinded site pharmacist or designee, independent of the study. A sponsor's pharmacist and drug accountability clinical research associates who were

independent of day-to-day operations of the study were unblinded to a subject's specific treatment assignment and responsible for checking the study drug supplies and accountability records at the sites and for confirming that subjects received the correct study agent at the correct dose level. The subject and all other study site, sponsor and CRO personnel remained blinded to the study agent received and to the results of certain biomarker measurements (i.e. aCL, anti-Sm, ANA, IgA and IgM, BLyS, and B cell subsets for C1056 subjects) and PK results.

Statistical methods

The primary analysis was a logistic regression analysis adjusted for baseline stratification factors. All statistical tests were 2-sided and performed at a significance level of 5% unless otherwise specified. The baseline of a variable was defined as the value of the variable measured at Day 0 prior to dosing, unless specified otherwise. If a Day 0 value was not available, the last available value prior to Day 0 was to be used. Patients discontinuing prior to the Week 52 visit were to be counted as failures in the primary responder analysis.

Unless otherwise specified, all analyses were performed on a modified intention-to-treat (mITT) population. The mITT population was defined as the subset of all randomized subjects who received at least one dose of study agent. The mITT analysis was performed according to the treatment that a subject was randomized to receive, regardless of the actual treatment received.

For the primary analysis of the primary endpoint a step-down sequential procedure was to be used to control the type 1 error. First the high dose treatment group was to be compared to placebo, and only if this comparison was statistically significant (2-sided alpha=0.05), the low dose would be compared to placebo (2-sided alpha=0.05).

Subgroup analyses for the primary endpoint according to the following factors were planned according to baseline SELENA SLEDAI score (≤9 vs ≥10); Race (African descent or indigenous-American descent (AIA) vs other); Baseline proteinuria level (<2 g/24 hour vs ≥2 g/24 hour equivalent); Baseline anti-dsDNA (≥30 IU/mL vs <30 IU/mL), Baseline prednisone dose level (≤7.5 mg/day vs >7.5 mg/day), Baseline C3 levels (normal/high vs low), Baseline C4 levels (normal/high vs low), Region.

Additional exploratory subgroup analyses by age, gender, baseline medications, baseline BILAG, baseline SELENA-SLEDAI score (≤ 12 vs ≥ 13), race, baseline ANA, anti-Sm, BLyS, steroid use were performed.

Results of Study C1056 (BLISS-76)

Participant flow

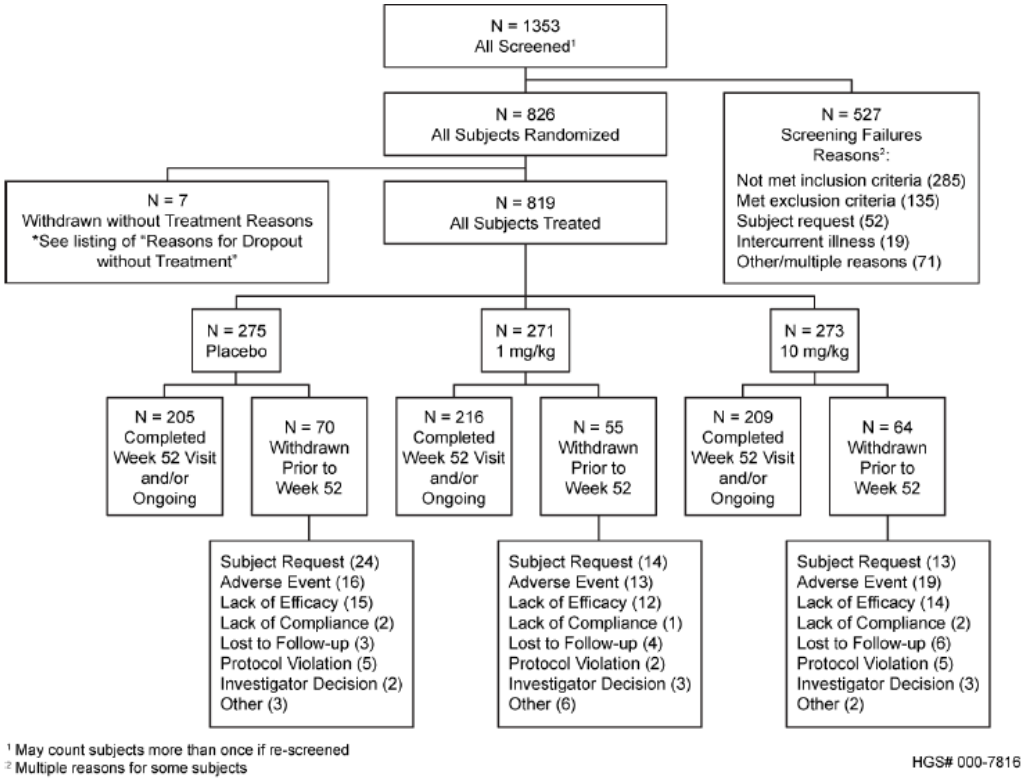


Figure Summary of subject disposition (Study C1056)

The overall rate of premature discontinuation of study agent was 26%, 20%, and 23% in the placebo group, 1 mg/kg, and 10 mg/kg belimumab groups, respectively. The most frequent reasons for discontinuing study agent were subject request, AE, and lack of efficacy.

Recruitment

Patients were recruited in a total of 136 study centers across Europe (62), North America (65) and Latin America (9). The study period was from 8 February 2007 (1st subject randomized) to 4 March 2010 (last subject complete 8-week follow-up).

Conduct of the study

The protocol for study C1056 was amended twice. The main purpose of Amendment 01 was to correct an error noted in the primary efficacy analysis and to modify the SELENA SLEDAI scoring of proteinuria at screening. Amendment 02 introduced a modification of the immunogenicity testing schedule to maintain the study blind; furthermore, some exclusion criteria were revised and previous IVIG administration as an indication for prophylaxis prior to administration of belimumab was added.

Baseline data

Baseline demographics

Subject demographics were generally comparable across treatment groups. The population in this study was predominantly white (70%). As expected, most subjects were female (93%). The mean age was 40 years (range 18-73), with only 2.0% of subjects 65 years or older. Subjects 45 years old and younger accounted for 67% of subjects, >45 to<65 years 31%. Subjects were randomized and treated at 136 sites across 19 countries (USA/Canada 53%, West Europe/Israel 25%, Eastern Europe 11.4%, others 10%). 70% of the patients were Caucasian, 14.4% were black/African American, 13% Natives from Alaska/America).

Baseline Disease Characteristics – Clinical measures

The mean duration of SLE was similar across groups (7.5 years in all groups).

Overall, the baseline level of disease activity was relatively high, with a mean score of 9.7 and approximately 51% of subjects presenting with a SELENA SLEDAI score of 10 points or greater. However, some imbalances in baseline disease activity between the belimumab and placebo groups were seen. A slightly higher number of subjects in the belimumab groups had low disease activity compared with the placebo group as measured by BILAG flare, and SLE flare index (SFI).

The number of subjects with SELENA SLEDAI scores of 0-3 at baseline (thereby making the subject unable to achieve a response of ≥4 points) was slightly imbalanced at 3, 5, and 8 in the placebo, 1 mg/kg, and 10 mg/kg belimumab groups, respectively.

Baseline disease characteristics – Biomarker measurements

Subjects who had either a positive ANA titer (≥1:80) or a positive anti-dsDNA result (≥30 IU/mL) were balanced across treatment groups. Detectable BLyS levels were present in 99% of all subjects. Once subjects are dosed with belimumab, high levels of circulating belimumab do not allow accurate measurement of free BLyS; therefore, on-treatment data were not considered informative and were not analyzed.

A few differences in baseline disease characteristics among the groups were noted. The proportion of subjects who were CRP positive (> 3 mg/L) was higher in the 1 mg/kg group (46%) compared with the placebo group (35%) (p = 0.0129).

Baseline Concomitant Medications

The most common (>10% in all groups) concomitant medications for SLE at baseline included the following: glucocorticoids (76%), antimalarials (63%), other immunosuppressives (56%), NSAIDs (41%), angiotensin pathway antihypertensives (25%), and HMG CoA reductase inhibitors (10%) and with balanced usage across treatment groups with a few exceptions. More subjects in the placebo group were receiving glucocorticoids (77% vs. 73%) as well as NSAIDs (43% vs. 37%) at baseline compared with the 10 mg/kg group. Also, within the therapeutic class of "other immunosuppressant," there was a difference noted between the placebo group and the 10 mg/kg group in the use of methotrexate (22% in placebo vs. 14% in 10 mg/kg).

Numbers analysed

All subjects (including those with dosing errors) were analyzed according to their randomized group.

In Study C1056, a total of 1,353 subjects were screened to yield 826 randomized subjects of whom 819 received at least 1 dose of study agent (mITT).

Around 630 (77%) of patients in all treatment groups completed the 52 weeks of treatment. The overall rate of premature discontinuation of study agent was 26%, 20%, and 23% in the placebo group, 1 mg/kg, and 10 mg/kg belimumab groups, respectively. The most frequent reasons for discontinuing study agent were subject request (8.7%, 5.2%, 4.8% in placebo, 1 mg/kg and 10 mg/kg group, respectively), AE (5.8%/4.8%/7.0%), and lack of efficacy (5.5%/4.4%/5.1%).

Outcomes and estimation for Study C1056

Results of Primary endpoint – SRI at week 52

A significant difference between the 10 mg/kg group and the placebo group was shown for the primary endpoint. The addition of belimumab 10 mg/kg to standard therapy yielded 9.41% more responders as compared to the placebo group (i.e. standard treatment only). Belimumab 1 mg/kg did not reach superiority versus placebo, but the magnitude of response was similar to that of the 10 mg/kg dose and numerically higher than placebo.

Table 7-1 Response at Week 52 (adjusted)

	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273
Response (primary efficacy analysis)	93 (33.8%)	110 (40.6%)	118 (43.2%)
Observed difference vs Placebo	-	6.77%	9.41%
OR (95% CI)[1] vs placebo	-	1.34 (0.94, 1.91)	1.52 (1.07, 2.15)
P-value[1]	-	0.1041	0.0207

[1] Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (AIA vs other).

Results for the components of the primary efficacy endpoint (SRI)

Belimumab 10 mg/kg demonstrated significant improvement over placebo for the response component of 4-point reduction in SELENA SLEDAI (p=0.0062) only. Thus, the effect was driven by the reduction in disease activity as measured by the SELENA-SLEDAI score with no differences in the other components of the primary endpoint. One would expect that the improvement in disease activity should be accompanied by better results also in PGA and BILAG scores, as these are more reliable measures of the disease activity control and its clinical translation. On the contrary, however, for the 1 mg/kg dose statistical significance was achieved for the PGA and BILAG components, but not for SELENA SLEDAI (Table below).

Table 7-2 The 3 components of response at Week 52 (adjusted)

	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273
4-point reduction in SELENA SLEDAI	98 (35.6%)	116 (42.8%)	128 (46.9%)
OR (95% CI)[1] vs placebo		1.36 (0.96, 1.93)	1.63 (1.15, 2.32)
P-value[1]		0.0869	0.0062
No worsening in PGA	173 (62.9%)	197 (72.7%)	189 (69.2%)
OR (95% CI)[2] vs placebo		1.60 (1.11, 2.30)	1.32 (0.92, 1.90)
P-value[2]		0.0120	0.1258
No New 1A/2B BILAG domain scores	179 (65.1%)	203 (74.9%)	189 (69.2%)
OR (95% CI)[3] vs placebo		1.63 (1.12, 2.37)	1.20 (0.84, 1.73)
P-value[3]		0.0108	0.3193

1 Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (AIA vs other).

2 Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline PGA.

3 Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline BILAG domain involvement (at least 1A/2B vs at most 1B).

One major reason for being classified as having a lack of response was medication failures. Subjects who required changes in background SLE medications beyond those permitted by protocol were declared treatment failures/non-responders. An unbalance between the groups was observed in that respect, with more subjects in the placebo group being classified as medication failures. This group included subjects who met all 3 response criteria indicating that a response could be achieved by increasing SOC.

Table 7-3 Disposition of response at Week 52 (adjusted)

	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273
Response	93 (33.8%)	110 (40.6%)	118 (43.2%)
No response	182 (66.2%)	161 (59.4%)	155 (56.8%)
Dropout[1] - not a medication failure	43 (15.6%)	40 (14.8%)	45 (16.5%)
Medication failure[2]	47 (17.1%)	24 (8.9%)	27 (9.9%)
< 4 point reduction in SS[3]	87 (31.6%)	91 (33.6%)	73 (26.7%)
≥ 4 point reduction in SS with the following[3]:	5 (1.8%)	6 (2.2%)	10 (3.7%)
Worsening in PGA only[3]	4 (1.5%)	4 (1.5%)	4 (1.5%)
New 1A/2B BILAG only[3]	1 (0.4%)	2 (0.7%)	6 (2.2%)
Both worsening in PGA and new 1A/2B BILAG[3]	-	-	-

1 Subjects who withdrew early and had no data in the Day 364 +/- 28 day window.

2 Includes subjects who withdrew early and subjects who met all 3 response criteria at Week 52 but took a protocol-prohibited or restricted medication or dose.

3 In subjects who did not dropout and were not medication failures.

To further elucidate this issue and to clarify whether a similar responder rate could be achieved by a more optimized baseline treatment, the applicant was requested during the assessment procedure to

perform additional responder analyses of the primary endpoint. The additional responder analyses should allow different levels of adjustment of concomitant medication without subjects being classified as having lack of response.

The results of those analyses as provided by the Applicant are summarized in the table below where any medication violation was allowed.

Table 3 Week 52 SRI response without medication failure rules

	C1056			C1057		
	Placebo	1mg/kg	10mg/kg	Placebo	1mg/kg	10mg/kg
Response (%)	37.1%	43.2%	45.4%	45.3%	51.7%	59.0%
OR (95% CI)		1.3 (0.9, 1.8)	1.4 (1.0, 2.0)		1.5 (1.0, 2.1)	1.8 (1.3, 2.6)
P value		0.1556	0.0429		0.0292	0.0007

Source Table 2.5 and 2.6, Figures 2.5 and 2.6 m5.3.5.3

Results for Major secondary endpoints (C1056)

The results of the major secondary endpoints in study C1056 are summarized in the table below.

Only in one of the major secondary endpoints (i.e. ≥4 point reduction from baseline in SELENA SLEDAI score) a significant improvement over placebo was shown for the recommended dose of 10 mg/kg. No dose-response relationship was identified.

Reductions (indicating improvement) in mean percent change and mean change from baseline in PGA at Week 24 were comparable across groups with no significant differences. The mean percent change was -26.18, -28.14 and -27.57 in the placebo, 1mg/kg group and 10mg/kg group, respectively.

In the patient reported outcome (mean change in SF-36 Health Survey PCS score at Week 24) no differences were seen between active and placebo groups (p=0.3848 in the 1mg/kg group, p=0.6601 in the 10mg/kg group).

Table. Results for major secondary efficacy endpoints – C1056

	Placebo N=275	**1 mg/kg N=271**	**10 mg/kg N=273**
SELENA SLEDAI ≥4point reduction from baseline at Week 52			
Response	98 (35.6%)	116 (42.8%)	128 (46.9%)
Observed difference vs placebo	-	7.17%	11.25%
OR (95% CI)1 vs placebo	-	1.36 (0.96, 1.93)	1.63 (1.15, 2.32)
P-value[1]	-	0.0869	0.0062
PGA change from baseline at Week 24			
Mean ± SE	-0.49 ± 0.04	-0.47 ± 0.04	-0.44 ± 0.03
Median (Min, Max)	-0.51 (-2.10, 1.53)	-0.42 (-2.40, 1.68)	-0.42 (-2.13, 1.38)
LS Mean ± SE[2]	-0.49 ± 0.05	-0.49 ± 0.06	-0.48 ± 0.05
Treatment differences (95% CI)[2] vs placebo	-	-0.00 (-0.09, 0.09)	0.01 (-0.08, 0.10)
P-value[2]	-	0.9545	0.7987
Prednisone reduction by ≥ 25% from baseline to			

≤7.5 mg/day during Weeks 40 through 52[3]			
N	126	130	120
Response	16 (12.7%)	25 (19.2%)	20 (16.7%)
Observed difference vs placebo	-	6.53%	3.97%
OR (95% CI)[1] vs placebo	-	1.57 (0.78, 3.14)	1.26 (0.61, 2.60)
P-value[1]	-	0.2034	0.5323
SF-36 PCS score change from baseline at Week 24			
N	274	270	269
Mean ± SE	3.36 ± 0.51	3.78 ± 0.46	3.22 ± 0.43
Median (Min, Max)	3.03 (-27.48, 26.62)	3.21 (-20.75, 29.05)	2.66 (-23.57, 25.49)
LS Mean ± SE[2]	5.63 ± 0.74	6.16 ± 0.75	5.36 ± 0.72
Treatment differences (95% CI)[2] vs placebo	-	0.53 (-0.67, 1.74)	-0.27 (-1.48, 0.94)
P-value[2]	-	0.3848	0.6601

1 Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs other).

2 All statistics, including the difference in LSM (least square means), were from ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for the covariates in footnote 1 and baseline PGA score.

3 Includes only subjects with baseline prednisone > 7.5 mg/day.

No clinically relevant benefit in regard to time to first flare or frequency of flares could be shown for the recommended treatment dose of belimumab. Although numerically shorter in the belimumab groups, the median time to 1st response (112-113 days) was not significantly different from placebo (119 days). No significant difference were seen for the recommended treatment dose of 10 mg/kg as compared to placebo in percentage of subjects whose average prednisone dose has been reduced by ≥25% from baseline to ≤7.5 mg/day during Weeks 40 through 52 and no dose-response relationship was seen.

Response rate at Week 76 in study C1056

In study C1056, placebo-controlled treatment with belimumab was continued through 18 month. Although numerically higher (6%) in the 10 mg/kg group, the result for SRI was no longer statistically significant at Week 76. Similar results were achieved with regard to reduction of average prednisone dose and flares with small numerical differences not reaching statistical significance for the proposed treatment dose (10 mg/kg belimumab).

As observed at Week 52, subjects with higher baseline disease or serological activity tended to respond better to belimumab, relative to placebo at Week 76, than did subjects with lower degrees of activity.

Table 3-3 Response at Weeks 52 and 76 (adjusted)

	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273
Week 52 Response (primary efficacy endpoint)	93 (33.8%)	110 (40.6%)	118 (43.2%)
Observed difference vs Placebo	-	6.77%	9.41%
OR (95% CI)[1] vs placebo	-	1.34 (0.94, 1.91)	1.52 (1.07, 2.15)
P-value[1]	-	0.1041	0.0207
Week 76 Response (major secondary endpoint)	89 (32.4%)	106 (39.1%)	105 (38.5%)
Observed difference vs Placebo	-	6.75%	6.10%
OR (95% CI)[1] vs placebo	-	1.34 (0.94, 1.91)	1.31 (0.92, 1.87)
P-value[1]	-	0.1050	0.1323

[1] Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (AIA vs other).

Table 3-16 Prednisone reduction by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 64 through 76[1]

	Placebo N = 126	1 mg/kg N = 130	10 mg/kg N = 120
Response[2]	22 (17.5%)	35 (26.9%)	29 (24.2%)
Observed difference vs placebo		9.46%	6.71%
OR (95% CI)[3] vs placebo		1.76 (0.96, 3.23)	1.43 (0.76, 2.68)
P-value[3]		0.0699	0.2686

[1] Includes only subjects with baseline prednisone > 7.5 mg/day.

[2] Any subject who withdrew from the study prior to the Day 532 (Week 76) visit, missed the Day 532 (Week 76) visit (± 28 day window allowed), and/or received a protocol-prohibited medication or a dose of allowable (but protocol-restricted) medication that resulted in treatment failure designation prior to the Day 532 (Week 76) visit was considered a treatment failure for prednisone reduction.

[3] Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates including baseline prednisone level, baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (AIA vs other).

Time to first overall flare was evaluated over 76 weeks and the proportion of patients with flares, and severe flares, was high in all treatment groups.

Ancillary analyses

Numerous pre-planned subgroup analyses have been performed by the Applicant. Overall, the response rate in subgroups was generally consistent with those observed in the overall population. A significant treatment-by-subgroup interaction for both belimumab treatment groups vs. placebo was observed for the race stratification factor (AIA race vs. other). The treatment-by-race interaction was driven by a differential response rate among placebo-treated subjects (49% for subjects of AIA race vs. 28% for subjects of other race) as the response rates among the belimumab 1 and 10 mg/kg subjects were comparable in both subgroups (40-44%). In the black subgroup, which comprises approximately one half of the AIA subgroup, the week 52 response was 39%, 30% and 33% in the placebo, 1 mg/kg, and 10 mg/kg groups respectively. During the procedure the Applicant was requested to present these data in detail and discuss on the causes and potential implications in terms of applicability of the results to the EU population.

In its response, the Applicant postulated that the differences observed in the effect of belimumab across races (particularly the lower effect in black patients) might be explained by differences in baseline disease activity rather than on true differences in the treatment effect explained by the race itself. In addition, the Applicant will conduct a specific study in black patients in the post-marketing setting.

To address concerns regarding the modest benefit/effect observed, particularly in study C1056, additional analyses were requested to further elucidate the magnitude of the treatment effect, maintenance of effect over time and whether or not belimumab would provide true clinical benefit when used as add on treatment in patients with optimized SOC.

An alternative responder analysis utilizing a more stringent endpoint was requested. The alternative responder analysis required a reduction of at least 6 point or a score ≤2on the SLEDAI component. The result of this analysis showed an effect size similar to or more pronounced than the results for the protocol specified primary endpoint (4 point improvement) (Table below). In particular, a statistically significant difference was observed at week 76.

Table. Adjusted relative risks and risk differences for an SRI response using a 6 point reduction or score of less than 2 in SELENA SLEDAI

	Week 52			**Week 76**		
C1056	Placebo N=275	1mg/kg N=271	10mg/kg N=273	Placebo N=275	1mg/kg N=271	10mg/kg N=273
Response (%)	57 (20.73%)	80 (29.52%)	88 (32.23%)	58 (21.09%)	75 (27.68%)	83 (30.40%)
RR (95% CI) P-value[1]		1.4 (1.05,1.87) p=0.0212	1.55 (1.17,2.06) p=0.0023		1.3 (0.97,1.75) p=0.0762	1.45 (1.09,1.93) p=0.0106
Adj Risk Difference (95% CI) P-value[2]		7.68 (0.8,14.55) p=0.0286	9.82 (2.76,16.87) p=0.0064		5.43 (-1.43,12.28) p=0.1208	8.18 (1.15,15.21) p=0.0225

[1] Relative risk (95% confidence interval) and p-value were from a log binomial model for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (<=9 vs >=10), baseline proteinuria level (<2g/24hour vs >=2g/24 hour equivalent) and race (African descent or indigenous-American descent vs other)

[2] Adjusted risk difference (95% confidence interval) and p-value were from a binomial regression comparing each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (<=9 vs >=10), baseline proteinuria level (<2g/24hour vs >=2g/24 hour equivalent) and race (African descent or indigenous-American descent vs other)

To further demonstrate the robustness of the primary efficacy analysis the applicant was requested to present cumulative distribution plots for the percent change in SELENA SLEDAI score, which represent the primary measure of efficacy in the composite endpoint SRI.

Consistent with the additional analyses, a 10-15 percentage difference between belimumab 10 mg and placebo was demonstrated for a wide range of improvement on the SELENA SLEDAI component of the primary endpoint.

Similarly the difference between 10 mg/kg and placebo was more pronounced in subjects with baseline SELENA SLEDAI score >10, and anti-dsDNA >30 IU/mL. These findings indicate a better treatment effect in subjects with high disease activity.

To further elucidate the issue of diminished effect over time, efficacy was evaluated in certain high activity subgroup, selected by the Applicant. The SRI response were analysed in each of these following baseline subgroups; SELENA SLEDAI >10, Positive anti-dsDNA and low C3 or low C4 (low C), Low C and use of corticosteroids, and Low C.

In these high activity subgroups the magnitude of effect at week 76, was more pronounced (about 8 to 12 percentages) than seen for the overall study population.

One *post-hoc* exploratory subgroup (baseline steroid use) yielded a significant treatment-by-subgroup interaction for the comparison of 10 mg/kg group vs. placebo. Response rates in subjects taking steroids at baseline were 33%, 39%, and 47% in the placebo, 1 mg/kg, and 10 mg/kg groups, respectively, while response rates in subjects not taking steroids at baseline were 38%, 45%, and 33%, respectively.

Results of Study C1057 (BLISS-52)

Participant flow

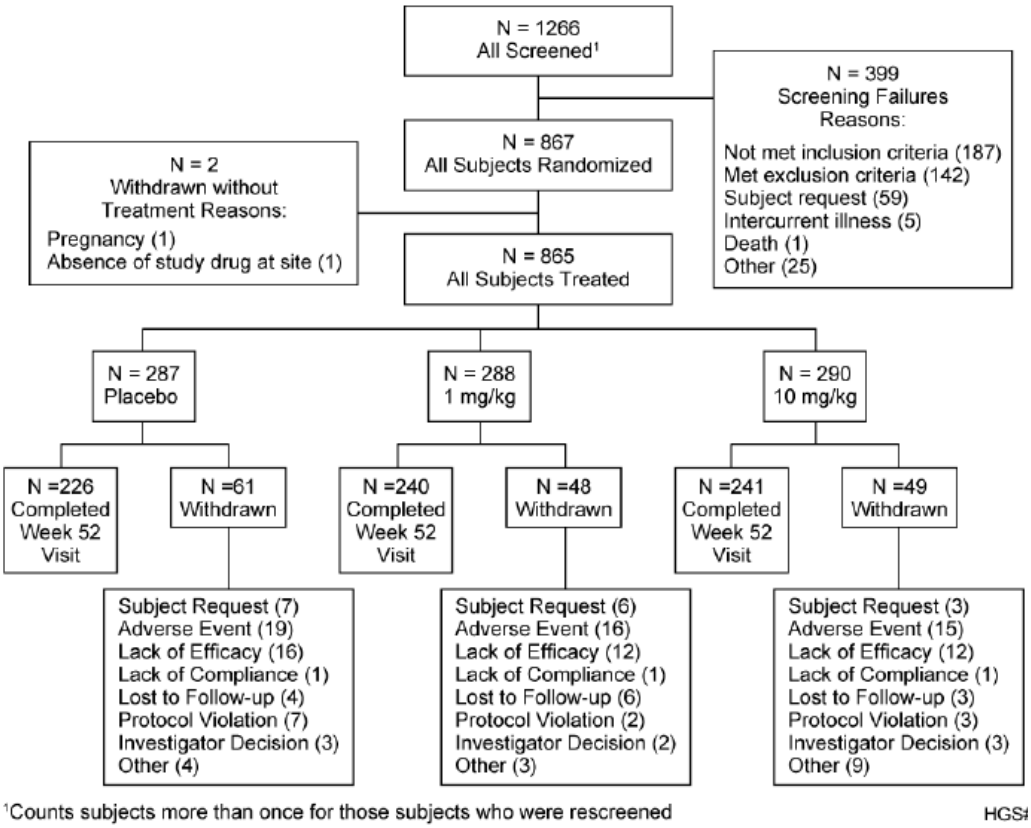


Figure Summary of subject disposition (C1057)

Recruitment

Patients were recruited in a total of 92 study centers across Europe (11), Asia Pacific (41) and Latin America (40). The study period was from 25 May 2007 (1st subject randomized) to 19 May 2009 (last subject complete 8-week follow-up).

Conduct of the study

The protocol for study C1057 was amended twice. The main purpose of Amendment 01 was to correct an error noted in the primary efficacy analysis and to modify the SELENA SLEDAI scoring of proteinuria at screening. Amendment 02 introduced modifications to the follow-up immunogenicity testing to maintain the study blind as well as some modifications to the exclusion criteria and variables to the secondary efficacy analysis.

Baseline data

Baseline demographics

Subject demographics were generally comparable across treatment groups. The population was predominantly Asian (38%), Alaska Native or American Indian from North/Central/South America (32%), and white (27%) with only few black subjects enrolled (4%). As expected, most subjects were female (95%). The mean age was 36 years (range 18-71 years), with 1.3% of subjects 65 years or older. Subjects ≤45 accounted for 82% of subjects, and >45-<65 for 18%.

With regard to race, study C1057 differed from study C1056 which included more Black African American and Caucasians and less Alaska native or American Indian subjects.

Baseline Disease Characteristics

The mean duration of SLE was 5.9 years in the placebo group compared with 5.0 years in each belimumab group. Otherwise, treatment groups were well balanced. The baseline level of disease activity was relatively high, with approximately 53% of subjects presenting with a SELENA SLEDAI score of 10 points or greater and a mean score of 9.8.

According to the index, the most common signs and/or symptoms that subjects presented with at baseline in all groups were increased DNA binding (74%), low complement (66%), rash (62%), arthritis (59%), alopecia (52%), mucosal ulcers (21%), and proteinuria (17%). Likewise, moderate to severe BILAG organ system involvement at baseline (A or B score) was similar in the belimumab and placebo groups, with the most common organ systems involved including mucocutaneous (59%), musculoskeletal (53%), hematology (19%), and renal (14%).

At Day 0, a positive ANA titer (≥1:80) was present in 94% of subjects, while a positive anti-dsDNA result (≥ 30 IU/mL) was present in 75% of subjects. A total of 98% subjects were positive for ANA and/or anti-dsDNA. Complement levels (C3 and C4) were less than the lower limit of normal (LLN) in 49% and 59% of subjects, respectively. Detectable BLyS levels were present in 97% of subjects. CRP was positive (>3mg/L) in 40% of patients at baseline

Baseline Concomitant Medications

The most common concomitant medications for SLE at baseline included the following: glucocorticoids (96%), antimalarials (67%), other immunosuppressives (42%), with balanced usage across treatment groups. More subjects in the placebo group (70%) were receiving antimalarials compared with the 10 mg/kg group (64%). Approximately 70% of subjects in each belimumab group were receiving systemic corticosteroids at a prednisone or prednisone-equivalent dose >7.5 mg/day at baseline compared with 67% of placebo subjects.

Numbers analysed

In total, 1,266 subjects were screened to yield 867 randomized subjects of whom 865 received at least one dose of study agent (mITT): 287 subjects in placebo group, 288 to the 1 mg/kg group, and 290 to the 10 mg/kg group.

The overall rate of premature discontinuation of study agent was 21% in the placebo group and 17% for each of the 1 mg/kg and 10 mg/kg belimumab groups. The most frequent reasons for discontinuing study agent were AE (6.6% v.s.5.2%) and lack of efficacy (5.6% vs. 4.1%) in the placebo and 10 mg/kg group, respectively.

Outcomes and estimation for Study C1057

Results of Primary endpoint – SRI at week 52

The number of responders was significantly superior to placebo in both the 10 mg/kg and the 1 mg/kg belimumab group. The 10 mg/kg dose of belimumab demonstrated superiority vs. placebo (all p-values <0.003) in each of the sensitivity analyses (LOCF, PP, Completer response). In this study, the magnitude of the treatment effect in the 10 mg/kg group was greater than what was observed in study C1056.

Table 7-1 Response at Week 52 (adjusted)

	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290
Response (primary efficacy analysis)	125 (43.6%)	148 (51.4%)	167 (57.6%)
Observed difference vs Placebo	-	7.83	14.03
OR (95% CI)[1] vs placebo	-	1.55 (1.10, 2.19)	1.83 (1.30, 2.59)
P-value[1]	-	0.0129	0.0006

[1] Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs other).

Results for the components of the primary efficacy endpoint (SRI)

Both 1 mg/kg and 10 mg/kg belimumab demonstrated significant improvement over placebo for the SELENA SLEDAI and PGA component for the responder index. Differences for the component "no new BILAG 1A/2B domain scores" was significant in the 10 mg/kg group but not for the 1 mg/kg group.

Both 1 mg/kg and 10 mg/kg belimumab demonstrated significant improvement over placebo for the SELENA SLEDAI and PGA component. Differences for the component "no new BILAG 1A/2B domain scores" was significant in the 10 mg/kg group but not for the 1 mg/kg group. In contrast to study C1056 a tendency of a dose-response relationship was seen.

For the SELENA SLEDAI component, which is the primary measure of efficacy, the difference between the 10mg/kg group and placebo was 12.3%. The difference in the other two components, representing no worsening, was smaller and the majority of study subject reach this criteria in all treatment groups.

The main reasons for lack of response in all groups was less than a 4 point reduction in SELENA SLEDAI followed by drop-out and medication failures. In each of these categories, there was a dose response trend with the highest percentage of subjects failing in the placebo group and the lowest percentage in the 10 mg/kg group.

Results for Major secondary endpoints (C1057)

The results of the major secondary endpoints in study C1057 are summarized in the table below.

Table. Results of major secondary efficacy endpoints – C1057

	Placebo N = 287	**1 mg/kg N = 288**	**10 mg/kg N = 290**
SELENA SLEDAI ≥4 point reduction from baseline at Week 52			
Response	132 (46.0%)	153 (53.1%)	169 (58.3%)
Observed difference vs placebo	-	7.13	12.28
OR (95% CI)1 vs placebo	-	1.51 (1.07, 2.14)	1.71 (1.21, 2.41)
P-value[1]		0.0189	0.0024
PGA change from baseline at Week 24			
Mean ± SE	-0.39 ± 0.03	-0.44 ± 0.03	-0.54 ± 0.03
Median (Min, Max)	-0.33 (-2.07, 0.99)	-0.42 (-2.04, 1.11)	-0.48 (-2.13, 1.62)
LS Mean ± SE[2]	-0.35 ± 0.04	-0.39 ± 0.04	-0.50 ± 0.04
Treatment differences (95% CI)[2] vs placebo	-	-0.05 (-0.13, 0.04)	-0.15 (-0.23, -0.07)
P-value[2]	-	0.2712	0.0003
Prednisone reduction by ≥ 25% from baseline to ≤7.5 mg/day during Weeks 40 through 52[3]			
N	192	204	204
Response	23 (12.0%)	42 (20.6%)	38 (18.6%)
Observed difference vs placebo	-	8.61	6.65
OR (95% CI)[1] vs placebo		1.89 (1.08, 3.31)	1.75 (0.99, 3.08)
P-value[1]		0.0252	0.0526
SF-36 PCS score change from baseline at Week 24			
N	286	283	284
Mean ± SE	3.64 ± 0.42	3.65 ± 0.43	3.58 ± 0.46
Median (Min, Max)	3.11 (-22.20, 32.93)	2.68 (-22.72, 33.80)	3.06 (-24.41, 30.24)
LS Mean ± SE[2]	3.26 ± 0.54	3.39 ± 0.53	3.34 ± 0.55
Treatment differences (95% CI)[2] vs placebo		0.13 (-0.95, 1.21)	0.08 (-1.00, 1.15)
P-value[2]		0.8127	0.8870

1 Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (<2 g/24 hour vs ≥2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs other).

2 All statistics, including the difference in LSM (least square means), were from ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for the covariates in footnote 1 and baseline PGA score.

3 Includes only subjects with baseline prednisone > 7.5 mg/day.

Percentage of subjects with >4 point reduction from baseline in SELENA SLEDAI score at Week52

As already presented, a significantly greater percentage of subjects in both the 1 mg/kg and in the 10 mg/kg belimumab vs. placebo groups had reduced SLE disease activity as measured by ≥4 point reduction from baseline in SELENA SLEDAI score.

At Week 24, a significantly higher percentage of subjects with SELENA SLEDAI reduction was observed or 10 mg/kg belimumab versus placebo (60% vs. 52%, p = 0.0434), which was maintained through Week 52. In the 1 mg/kg belimumab group, significant improvement over placebo was observed at Weeks 40 to 52.

Mean change/percent change in PGA at Week 24

Both belimumab groups achieved a significant reduction for percent change from baseline in PGA compared with placebo at Week 24.

Percentage of subjects whose average prednisone dose has been reduced by ≥25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52

The percentage of subjects whose average prednisone dose was reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52 was significantly higher in the 1 mg/kg group but only numerically higher in the 10 mg/kg group vs. placebo.

The mean number of cumulative days of daily prednisone dose ≤7.5 mg/day and/or reduced by 50% from baseline was significantly greater in the 10 mg/kg group vs. placebo by Week 40 and persisted to Week 52 and was numerically greater (difference >5 days) in the 1 mg/kg group vs. placebo by Week 36 and persisted to Week 52.

In contrast to study C1056, a small difference in prednisone reductions in favor of the active groups was seen over time.

Mean change in SF-36 Health Survey PCS score at Week 24

In the patient reported endpoint, mean change in SF-36 Health Survey PCS score at Week 24, no benefit could be demonstrated for the active groups (p=0.8127 in the 1mg/kg group and p=0.8870 in the 10 mg/kg group).

The median time to 1st response, although numerically shorter in the belimumab groups (84-85 days), was not significantly different from placebo (112 days). The percentage of subjects whose average prednisone dose was reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52 was significantly higher in the 1 mg/kg group (difference=8.61%, p=0.0252) but only numerically higher in the 10 mg/kg group (difference =6.65%, p=0.0526) vs. placebo.

Ancillary analyses

Subgroup analyses for pre-specified major subgroups

Response rates observed in the subgroups were generally consistent with those observed in the overall population. The only subgroup with a significant treatment-by-subgroup interaction for both belimumab treatment groups vs. placebo was baseline SELENA SLEDAI score. The difference in response rate in belimumab-treated groups vs. placebo was greater in subjects with baseline SELENA SLEDAI score ≥10.

Table 7-5 Primary Response at Week 52 by major subgroup

	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290
Baseline SELENA SLEDAI score (stratification factor)			
≤ 9 points	47/129 (36.4%)	55/149 (36.9%)	53/130 (40.8%)
≥ 10 points	78/158 (49.4%)	93/139 (66.9%)	114/160 (71.3%)
Interaction P-value[1]	-	0.0409	0.0312

[1] For treatment by subgroup interaction effect from logistic regression.

As for study C1056, an alternative responder analysis utilizing a more stringent endpoint was performed, requiring a reduction of at least 6 point or a score ≤2on the SLEDAI component (see Table below).

Table. Adjusted relative risks and risk differences for an SRI response using a 6 point reduction or score of less than 2 in SELENA SLEDAI

	Week 52		
C1057	Placebo N=287	1 mg/kg N=288	10 mg/kg N=290
Response (%)	85 (29.62%)	109 (37.85%)	129 (44.8%)
RR (95% CI) P-value[1]		1.41 (1.14,1.75) p=0.0017	1.52 (1.24,1.87) p<0.0001
Adj Risk Difference (95% CI) P-value[2]		8.49 (0.97,16.01) p=0.0269	12.5 (5,20) p=0.0011

[1] Relative risk (95% confidence interval) and p-value were from a log binomial model for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (<=9 vs >=10), baseline proteinuria level (<2g/24hour vs >=2g/24 hour equivalent) and race (African descent or indigenous-American descent vs other)

[2] Adjusted risk difference (95% confidence interval) and p-value were from a binomial regression comparing each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (<=9 vs >=10), baseline proteinuria level (<2g/24hour vs >=2g/24 hour equivalent) and race (African descent or indigenous-American descent vs other)

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table. Summary of Efficacy for trial C1056 (BLISS-76)

Title: A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 76-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006, LymphoStat-B™), a Fully Human Monoclonal Anti-BLyS Antibody, in Subjects with Systemic Lupus Erythematosus (SLE)			
Study identifier	HGS1006-C1056 (EudraCT Number: 2006–005177–21)		
Design	Phase 3, multi-center, randomized (1:1:1), double-blind, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		76 weeks not applicable not applicable
Hypothesis	Superiority; the response rate for 10 mg/kg belimumab group (or for both 1 mg/kg and 10 mg/kg belimumab groups) is superior to placebo		
Treatments groups	1 mg/kg		Standard therapy + 1 mg/kg belimumab; 72 weeks; N=271
	10 mg/kg		Standard therapy + 10 mg/kg belimumab; 72 weeks;N=273
	Placebo		Standard therapy + placebo; 72 weeks;N=275
Endpoints and definitions	Primary endpoint	Response rate (SRI[2]) at Week 52	- ≥4 point reduction from baseline in SELENA SLEDAI score, AND - No worsening (increase of <0.30 points from baseline) in PGA, AND - No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (i.e. at Week 52).
	Major secondary endpoint	RR at Week 76	Response rate at Week 76 (SELENA SLEDAI ≥4 point reduction and no worsening as measured by PGA and BILAG)
	Major secondary endpoint	≥4 point reduction in SS at Week 52	% of subjects with ≥4 point reduction in SELENA SLEDAI at Week 52
	Major secondary endpoint	PGA at Week 24	Mean change in PGA at Week 24
	Major secondary endpoint	CS reduction	% Subjects with prednisone (equivalent) reduction ≥25% from baseline to ≤7.5 mg/day during Weeks 40–52 (in subjects whose prednisone equivalent dose was >7.5 mg/day at baseline)
	Major secondary endpoint	SF-36	Mean change in SF-36 PCS at Week 24
Database lock	2 database locks (Week 52 and Week 76 analysis)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified intent to treat (mITT); Week 52 and 76		

[2] SRI – SLE responder index

Descriptive statistics and estimate variability **(Week 52 analysis)**	Treatment group	Placebo	1 mg/kg	10 mg/kg
	Number of subject	N=275	N=271	N=273
	Response rate (%)	33.8	40.6	43.2
	OR (95% CI) vs placebo		1.34 (094, 1.91)	1.52 (1.07, 2.15)

Effect estimate per comparison	Primary endpoint (Response at Week 52)	Comparison groups	10 mg/kg vs placebo
		Observed difference	9.41%
		P-value (logistic regression)	0.0207
		Comparison groups	1 mg/kg vs placebo
		Observed difference	6.77%
		P-value (logistic regression)	0.1041
	RR at Week 76	Comparison groups	10 mg/kg vs placebo
		Observed difference	6.10%
		P-value (logistic regression)	0.1323
		Comparison groups	1 mg/kg vs placebo
		Observed difference	6.75%
		P-value (logistic regression)	0.1050
	≥4 point reduction in SS at Week 52	Comparison groups	10 mg/kg vs placebo
		Observed difference	11.25%
		OR (95% CI)	1.63 (1.15, 2.32)
		P-value	0.0062
	PGA at Week 24	Comparison groups	10 mg/kg vs placebo
		Treatment differences (95% CI)	0.01 (-0.08, 0.10)
		P-value	0.7987
	CS reduction	Comparison groups	10 mg/kg vs placebo
		OR (95% CI)	1.26 (0.61, 2.60)
		P-value	0.5323
	SF-36	Comparison groups	10 mg/kg vs placebo
		Treatment differences (95% CI)	-0.27 (-1.48, 0.94)
		P-value	0.6601

Table. Summary of Efficacy for trial C1057 (BLISS-52)

Title: A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006, LymphoStat-B™), a Fully Human Monoclonal Anti-BLyS Antibody, in Subjects with Systemic Lupus Erythematosus (SLE)		
Study identifier	HGS1006-C1057 (EudraCT Number: 2006–005190-21)	
Design	Phase 3, multi-center, randomized (1:1:1), double-blind, placebo-controlled	
	Duration of main phase:	52 weeks
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable

Hypothesis	Superiority; the response rate for 10 mg/kg belimumab group (or for both 1 mg/kg and 10 mg/kg belimumab groups) is superior to placebo		
Treatments groups	1 mg/kg		Standard therapy + 1 mg/kg belimumab; 52 weeks; N=288
	10 mg/kg		Standard therapy + 10 mg/kg belimumab; 52weeks;N=290
	Placebo		Standard therapy + placebo; 52 weeks;N=287
Endpoints and definitions	Primary endpoint	Response rate (SRI[3]) at Week 52	- ≥4 point reduction from baseline in SELENA SLEDAI score, AND - No worsening (increase of <0.30 points from baseline) in PGA, AND - No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (i.e. at Week 52).
	Marjor secondary endpoint	≥4 point reduction in SS at Week 52	% of subjects with ≥4 point reduction in SELENA SLEDAI at Week 52
	Marjor secondary endpoint	PGA at Week 24	Mean change in PGA at Week 24
	Marjor secondary endpoint	CS reduction	% Subjects with prednisone (equivalent) reduction ≥ 25% from baseline to ≤7.5 mg/day during Weeks 40 – 52 (in subjects whose prednisone equivalent dose was > 7.5 mg/day at baseline)
	Marjor secondary endpoint	SF-36	Mean change in SF-36 PCS at Week 24

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Modified intent to treat (mITT); Week 52			
Descriptive statistics and estimate variability	Treatment group	Placebo	1 mg/kg	10 mg/kg
	Number of subject	N=287	N=288	N=290
	Response rate (%)	43.6	51.4	57.6
	OR (95% CI) vs placebo		1.55 (1.10, 2.19)	1.83 (1.30, 2.59)
Effect estimate per comparison	RR at Week 52	Comparison groups	10 mg/kg vs placebo	
		Observed difference	14.03	
		P-value (logistic regression)	0.0006	
		Comparison groups	1 mg/kg vs placebo	

[3] SRI – SLE responder index

		Observed difference	7.83
		P-value (logistic regression)	0.0129
	≥4 point reduction in SS at Week 52	Comparison groups	10 mg/ml vs placebo
		Observed difference	12.28
		OR (95% CI)	1.71 (1.21, 2.41)
		P-value	0.0024
	PGA at Week 24	Comparison groups	10 mg/ml vs placebo
		Treatment differences (95% CI)	-.015 (-0.23, -0.07)
		P-value	0.0003
	CS reduction	Comparison groups	10 mg/ml vs placebo
		OR (95% CI)	1.75 (0.99, 3.08)
		P-value	0.0526
	SF-36	Comparison groups	10 mg/ml vs placebo
		Treatment differences (95% CI)	0.08 (-1.00, 1.15)
		P-value	0.8870

Biomarkers in Phase 3 studies

Change in biomarkers, supporting the proposed immunomodulating function of belimumab, was shown in both Phase 3 trials. Findings suggesting that subjects with dysregulated B-cell function, resulting in autoantibody production may benefit from belimumab treatment.

Immunoglobulins

Reductions in immunoglobulins induced by belimumab were seen with beginning at Week 8. Immunoglobulin levels in the placebo group remained relatively stable over time.

At Week 52 the IgG median percent reduction, in Study C1056, was approximately 14% in both belimumab groups, while IgG remained stable in the placebo group (decrease of 0.8%; p<0.0001). In C1057 the results were similar, with median percent IgG reductions of 14% and 16% in the 1 and 10 mg/kg groups, respectively, compared with 3.6% reduction in the placebo group (p<0.0001).

For IgM, the median percent reductions observed were 28% and 31% in the 1 mg/kg and 10 mg/kg groups, respectively, while values remained stable in the placebo group (decrease of 0.5%; p<0.0001). The IgM median percent reduction in Study C1057 was similar to that observed in C1056, 28% and 30% in the 1 and 10 mg/kg belimumab groups, respectively, compared with a decrease of 3.2% with placebo (p<0.0001). Likewise, significant reductions in IgA were observed by Week 52, median percent reductions in IgA ranged from 16-18% with belimumab compared with median percent reductions of 0.7% to 2.7% with placebo (p<0.0001 for all comparisons).

Autoantibodies

Significant decreases in anti-dsDNA with belimumab were observed from Week 8, which persisted through Week 52. The median percentage reduction in anti-dsDNA levels at Week 52 in the pooled dataset was 18-19% for belimumab with no change in the placebo group (p<0.0001).

In addition to the effects observed in anti-dsDNA, a higher proportion of subjects receiving belimumab converted from seropositive to seronegative status for ANA, anti-Sm and anti-ribosomal-P antibodies.

Complement

There was a dose response effect with significant improvement in C3 and C4 from Week 4 with the belimumab 10 mg/kg dose that was sustained to Week 52. For C3 in the pooled dataset, 17%, 26% and 38% of subjects in the placebo, 1 mg/kg and 10 mg/kg belimumab groups with low complement at baseline had their complement levels recover to above the LLN by Week 52. For C4, these rates were 18%, 35%, and 44%, respectively.

B- and T-cell subsets

B- and T-cell subsets were evaluated only in C1056 in the Phase 3 program. The effect of belimumab on the overall population of B cells was a significant reduction compared with placebo, seen with both CD19+ and CD20+ B cells at Week 24 and continuing through Week 52. At Week 24, the median reduction in CD19+ B cells was 33% and 29% with 1 mg/kg and 10 mg/kg belimumab treatment, while the reduction of placebo was approximately 3%; at Week 52 the median reduction with belimumab was 48% compared to 10% with placebo. Median reductions in CD20+ B cells were similar.

Analysis performed across trials (pooled analyses and meta-analysis)

Due to the reduced sample size in subgroups, subgroups analyses are presented pooled.

Pooled analyses of the efficacy results from the two pivotal Phase 3 trials have been performed. The pattern of results for the pooled data on Primary and Major secondary endpoint was overall similar as seen for the individual studies.

Regional subgroups

There were differences in the response rate according to origin country, and differences in effect according to ethnicity cannot be ruled out. Patients from Eastern Europe as well as Americans excluding US/Canada had higher rates of response to belimumab as compared to patients from other regions. The Applicant was requested to present these data in detail and discuss on the causes and potential implications in terms of applicability of the results to the EU context (see table below).

Subjects in the US/Canada had lower response rates in all 3 treatment groups compared with all other regions. This less robust response was believed by the Applicant to be related to the lower baseline disease activity in the US, as measured by multiple measures including SELENA SLEDAI, steroid use and serological activity, compared with other regions. Importantly, subjects in the US with higher disease activity (SELENA SLEDAI ≥ 10), respond similarly to subjects from other regions and to subjects overall across the two trials. These findings further support the hypothesis that response to belimumab is associated with greater baseline disease activity. Subjects with higher disease activity tend to have a more robust response.

Table 2.5-13 Primary Response at Week 52 by region-pooled

	Placebo N = 562	1 mg/kg N = 559	10 mg/kg N = 563
Overall	218 (38.8%)	258 (46.2%)	285 (50.6%)
Region			
Americas excl. US/Canada	88/175 (50.3%)	100/169 (59.2%)	102/172 (59.3%)
US/Canada	46/145 (31.7%)	59/155 (38.1%)	47/136 (34.6%)
Asia	40/103 (38.8%)	42/106 (39.6%)	58/115 (48.7%)
Western Europe/Israel/Australia	17/70 (24.3%)	25/68 (36.8%)	41/79 (51.9%)
Eastern Europe	27/69 (39.1%)	32/61 (52.5%)	39/61 (63.9%)

Clinical studies in special populations

To date, no studies in the paediatric population have been performed with belimumab.

No specific studies have been performed in elderly. Data on patients >65 years are limited to <1.6% of the population studied in clinical trials and the efficacy and safety of Benlysta in the elderly has not yet been established. This is reflected in the SPC, together with a statement that treatment of elderly patients is not recommended unless the benefits are expected to outweigh the risks. Furthermore, the limited data in elderly patients is included as important missing information in the RMP including the appropriate pharmacovigilance measures.

Supportive studies

Long-term continuation trials in SLE

The long-term continuation trials conducted with belimumab in SLE include LBSL99, C1066, and C1074. LBSL99 is the ongoing Phase 2 continuation trial for study subjects completing the Phase 2 study LBSL02. Studies C1066 and C1074 are ongoing Phase 3, multi-center, continuation studies to evaluate the long-term safety and tolerability of belimumab in subjects with SLE. The safety data obtained from these trials are discussed in the safety section below.

2.5.3. Discussion on clinical efficacy

A Phase 2 dose-response study conducted in subjects with active SLE evaluated belimumab doses of 1, 4 and 10 mg/kg, or placebo in combination with standard of care. The study failed to achieve superior efficacy in the co-primary endpoints defined as percent reduction in SELENA SLEDAI score at Week 24 and time to first SLE flare (SFI) over 52 weeks. The mean percent decrease in SELENA SLEDAI score at Week 24 was numerically better than placebo for the 1 and 10 mg/kg groups with an average of approximately 23% each, compared with 17% in the placebo group, but the difference did not reach statistical significance. No dose-response relationship was evident in the dose-range of 1 to 10 mg/kg. The 4 mg/kg group had a mean percent decrease of 11% which was numerically lower than placebo. Further, belimumab did not show benefit as measured by the pre specified major secondary endpoints.

While the Phase 2 study did not provide strong support for the efficacy of belimumab, a treatment effect was observed in post-hoc analyses in subjects with the certain baseline disease characteristics such as anti-dsDNA antibody positivity, low C3, low C4, and prednisone dose >7.5 mg/day at baseline. Based on this information the Phase 3 program was designed to include a patient population with these baseline characteristics.

Design and conduct of clinical studies

The design of the pivotal Phase 3 studies had been agreed in a formal scientific advice procedure with the CHMP and was overall considered acceptable. The inclusion criteria were considered well justified; the requirement of autoantibody positivity focused on patients with dysregulated B cell immunity. The use of more a strict SELENA SLEDAI score ensured the inclusion of patients with more severe disease profile than in the Phase 2 trial. The chosen exclusion criteria were considered reasonable from a clinical point of view as they excluded patients in need of a rapid onset and well established treatment for the control of their disease activity (e.g. active lupus nephritis or CNS disease).

For the efficacy evaluation, the Applicant presented a composite endpoint, the SLE responder index (SRI) which is composed of three established tools. In view of the complexity of SLE it was agreed that a single tool might not be sufficient to adequately assess disease activity of individual patients. Furthermore, it is important to show that any therapy that improves disease in one organ system does not worsen disease elsewhere. The SRI had been agreed in a scientific advice procedure, and CHMP endorsed the choice of the included components in the SRI.

Concomitant medication rules were agreed with FDA and EMA prior to initiation of the studies and are considered acceptable. Although some restrictions were established for CS use during the clinical trial, CS tapering was not a key objective of the study. However, CS tapering was a secondary endpoint and is considered a key variable for the overall assessment of the additional benefits of belimumab.

Efficacy data and additional analyses

Although both Phase 3 trials achieved a significant higher responder rate for the 10 mg/kg dose, overall the results in C1056 are less convincing and the results in study C1057 shows a more robust treatment difference between active and placebo groups. In study C1056, belimumab 10 mg/kg in addition to standard therapy yielded 9.41% more responders at Week 52 as compared to standard therapy only. In study C1057 14% more responders were seen.

The rather modest benefit shown in Study C1056 was mainly driven by the effect on a highly sensitive score (SELENA-SLEDAI) of disease activity, with a questionable dose-response effect and, more importantly, without a clear clinical translation on more straightforward interpretable variables (PGA, BILAG). This yielded a number of questions regarding the efficacy of belimumab and alternative analyses of the Phase 3 studies were requested by the CHMP during the assessment procedure.

An alternative responder analysis utilizing a more stringent endpoint was therefore performed that required a reduction of at least 6 point or a score ≤2 on the SLEDAI component. The results were similar to the results in the protocol specified analysis. To further demonstrate the robustness of the primary efficacy analysis the applicant was requested to present cumulative distribution plots for the percent change in SELENA SLEDAI score, which represent the primary measure of efficacy in the composite endpoint SRI. Consistent with the additional analyses, a 10-15 percentage difference between belimumab 10 mg and placebo was demonstrated for a wide range of improvement on the SELENA SLEDAI component of the primary endpoint.

Following the initial evaluation of data, efficacy on immunological parameters was established but there was doubt whether the small benefit observed on the SELENA-SLEDAI score would translate into clinical benefit. To clarify to which extent efficacy was related to other criteria than improvement in immunological parameters, a responder analysis was performed in which patients with improvement in immunological parameters only were counted as non-responders. The presented results were consistent with the results of the primary analyses. Thus, the difference between groups is not only related to laboratory or immunological changes.

In both studies one major reason for being classified as having a "lack of response" was medication failures. Subjects who required changes in background SLE medication beyond that permitted by protocol were declared treatment failures/non-responders. An imbalance between the groups was observed in that respect as more subjects were classified as "medication failures" in the placebo compared to the active groups. To evaluate whether a similar responder rate could be achieved by optimizing baseline therapy, additional responder analyses were performed by the Applicant. The overall results were consistent with the results of the primary analyses. The imbalance in medication failures between active and placebo groups did not seem to have any major impact on the difference in responder rate.

Subgroup analyses showed a higher response rates in subjects with baseline SELENA SLEDAI score > 10 points. Further, an overall trend of higher response rate is also seen in subject with signs of more active disease at baseline (high baseline steroid use, low C3, C4 and anti-dsDNA >30IU/ml). This trend of higher response rate, was further demonstrated by additional analyses in certain high activity subgroups (SELENA SLEDAI>10, positive anti-dsDNA and low C3/C4, low C3/C4 and use of steroids, and low C3/C4). Based on the results in high activity subgroups it was concluded that an effect that could be of value for some patients had been demonstrated. During the procedure, the Applicants presented the efficacy results for the subgroup of patients with anti-dsDNA antibodies and low levels of C3 and/or C4. In the response it was demonstrated that for this subgroup the difference between belimumab 10mg/kg and placebo (19.8%) was almost doubled to the difference observed for the overall study population (11.8%) and a significant effect on SRI (12%) was maintained to week 76. A larger difference was also seen for other endpoints such as BILAG, PGA and severe flare.

The effect of belimumab has been shown in a population with mainly mucocutaneous and musculoskeletal involvement and the effect of belimumab on key target SLE organs has not been established. The reason for not including patients with active nephritis or CNS involvement in the Phase 3 trials seems justified as these patients require a rapid onset and well-established treatment for the control of disease activity; however, this does not change the fact that data in this aspect is insufficient for conclusions on belimumab effect on key target organs. A trial specifically evaluating safety and efficacy of belimumab in lupus nephritis patients is planned, but does not cover for the current lack of data in more vital organ domains. Therefore, CHMP concluded that the effect of belimumab has only been demonstrated in a patient population with mainly musculoskeletal, vascular, mucocutaneous and haematological involvement. Whether the observed modest effect would remain in patients with other key organ involvement (mainly renal and CNS) is unknown and is clearly pointed out in the SPC. Furthermore, a study to evaluate the efficacy and safety of belimumab in patients with lupus nephritis will be conducted as a post-approval commitment.

In study C1056, placebo-controlled treatment with belimumab was continued through 18 months (76 weeks). The result for SRI at Week 76 was not statistically significant and a difference of approximately 6% responders between the proposed treatment dose of 10 mg/kg and placebo was seen. Similar results were achieved with regards to reduction in average prednisone dose and flares, which showed small numerical differences not reaching statistical significance for the proposed belimumab dose.

The findings of C1056 at Week 76 raised concerns about maintenance of effect and the Applicant was requested to further substantiate long-term efficacy. To further elucidate the issue of diminished effect over time, efficacy was evaluated in certain subgroups of patients with high disease activity (SELENA SLEDAI >10, Positive anti-dsDNA and low C3 or low C4 (low C), Low C and use of corticosteroids, Low C). In these high activity subgroups the magnitude of effect at Week 76 was more pronounced than seen for the overall study population. Additionally, a sustained significant effect was shown at Week 76 in analyses with more strict response criteria which gives some support of a maintained effect.

The CHMP questioned the applicability of the baseline therapy and the high use of corticosteroids (CS) in the SLE studies. The chronic corticosteroid use may not be considered in line with current clinical practice in some EU Member States. Further discussion on the use of corticosteroids as part of standard of care in the treatment of SLE took place at an ad hoc expert meeting. At this meeting, the experts acknowledged the variability of CS use across Europe, which is caused by many factors including region, speciality of treating physician or type of treatment setting/centers. Furthermore, it was confirmed that the patients included in the belimumab Phase 3 trials were required to have active disease, i.e. were on CS by definition. There was broad agreement amongst the experts that a steroid sparing effect is of great importance and has a significant impact on the patient's quality of life.

In conclusion, the experts were not concerned with high use of CS in the belimumab clinical trials and did not consider the pattern of CS use to impact on the ability to extrapolate the study results to the intended EU target population.

Differences in the response rates varied according to race; however, the available data was considered insufficient to draw firm conclusions. CHMP therefore requested that the ad hoc expert group discuss the question whether the differences in magnitude of effect of Benlysta observed between races could be explained as a random finding or if racial factors could explain this difference in response. In their answer, the experts stated that differences in response across racial groups are known for other drugs used in SLE. According to the experts, however, this did not have a significant impact on the treatment decisions in clinical practice. Nevertheless, the experts confirmed that they would like to see further data with belimumab to elucidate this phenomenon. In conclusion, the issue of a possible difference in effect between ethnicities was not of concern to the experts as this is considered manageable in clinical practice.

Immunogenicity was observed relatively infrequently. However, as assays sensitivity for neutralizing antibodies and non-specific anti-drug antibody (ADA) are limited by the presence of active drug in the collected samples, insight in the true occurrence of neutralizing antibodies and non-specific anti-drug antibody in the study population is very limited. The risk of immunogenicity will continue to be assessed to further investigate a possible relationship between antibody formation and treatment outcomes and adverse events.

Additional expert consultation

Following a request from the CHMP, an Ad-Hoc Expert Meeting was convened on 30 March 2011 to provide advice on the CHMP list of questions adopted by the CHMP at its February 2011 meeting.

The experts were asked to comment on four questions/areas, namely the clinical relevance of the observed treatment effect of belimumab in the pivotal studies; the relevance of the effect seen in patients with higher disease activity and the feasibility to clinically define such a patient population; the applicability of baseline therapy and the extensive use of corticosteroids in the pivotal SLE studies, as well as the observed differences of effect of belimumab between ethnicities.

Regarding the clinical relevance of the observed treatment effect, the experts agreed that a moderate effect of belimumab has been seen on top of other therapies in a patient population that represents the majority of cases in clinical practice. It was noted that patients with more severe disease (i.e. renal, neurological manifestations) were excluded from the study; a greater need for additional/new treatment options was clearly seen in these more severe patients. A more pronounced effect was seen in a subgroup of patients with high disease activity (i.e. SELENA SLEDAI score at baseline ≥10, anti-dsDNA positive, low C3/C4).

While the experts considered the effect on flares (delayed time to first flare, reduced risk of severe flare) in this subgroup as of clinical importance, it was agreed that the available data on flare reduction was only indicative. It was acknowledged that the clinical development/study design was not intended for induction of remission, but rather maintenance therapy.

The experts acknowledged that fatigue is of specific relevance to patients who consider this the most debilitating aspect of the disease and thus has a great impact on quality of life. Methodologically the measurement of improvement in fatigue is difficult. Nevertheless, the data for belimumab suggest a beneficial effect on fatigue. The improvement in fatigue scores was again more pronounced in the subgroup of patients with high disease activity compared to the overall population. Further data on fatigue from studies was requested.

The experts concluded that generally efficacy of belimumab has been shown, if only a moderate one. While the expectation for the first biological drug for SLE may have been greater, also in view of the associated risks, the group agreed that the efficacy seen is clinically relevant for a certain subgroup of patients with high disease activity. The need to properly define this patient population has been emphasized.

However, the experts also stressed the need for further data on safety and efficacy of belimumab treatment in patients with severe manifestations (e.g. lupus nephritis, CNS). Furthermore, the experts felt that further data was needed about secondary responses (e.g. impact on antiphospholipid antibody levels). Given the currently available therapies, the need to generate more data on the potential use during pregnancy was considered of great relevance for medical practice.

Regarding the wording of the indication, in principle the experts concurred with an indication that restricts the use to patients with high disease activity. The experts agreed that ideally disease activity should be assessed using a validated disease index rather than laboratory values. The work currently ongoing in the academic setting was emphasised; at the same time the fact that these indices might not widely be used in clinical practice was acknowledged.

The proposal from the company to use laboratory tests (anti-dsDNA, low C3/C4) only to define disease activity, rather than questionnaire, was considered acceptable for the indication wording. In addition, some experts felt that it would be of value to also indicate in the indication wording the use of a validated disease index (e.g. SELENA SLEDAI, ECLAM) as an alternative for the assessment of disease activity since both indices were considered simple to use (in contrast to BILAG) and are used in clinical practice.

With regard to the wording for the target population the experts consider that the proposal has limitations as "standard therapy" is very difficult to define for a disease with such heterogeneous manifestations. However, the experts acknowledged that this population is the one used in the clinical studies and the proposal seems appropriate.

The recommendation to discontinue belimumab treatment in patients that do not show an improvement in disease control after 6 months was supported by the experts.

The experts acknowledged the variability of corticosteroid (CS) use across Europe. In addition to region, a number of additional factors influence the use CS, such as speciality of treating physician or treatment centers, specific organs affected as well as the patient's response. Furthermore, it was confirmed that the patients included in the belimumab trials were required to have active disease, i.e. were on CS by definition.

There was broad agreement amongst the experts that a steroid sparing effect is of great importance and has a significant impact on the patient's quality of life.

In conclusion, the experts were not concerned with high use of CS in the belimumab clinical trials and did not consider the pattern of CS use to impact on the ability to extrapolate the study results to the intended EU target population.

The differences in the magnitude of effect between ethnicities were noted. The experts stated that differences in response across racial groups are known for other drugs used in SLE and that all races are affected by SLE.

According to the experts, however, this did not have a significant impact on the treatment decisions in clinical practice. Nevertheless, the experts confirmed that they would like to see further data with belimumab to elucidate this phenomenon.

In conclusion, the issue of a possible difference in effect between ethnicities was not of concern to the experts as this is considered manageable in clinical practice. The experts welcomed the company's commitment to conduct a post-approval study to address this question.

2.5.4. Conclusions on the clinical efficacy

The efficacy of belimumab as an add-on therapy in the treatment of patients with active, autoantibody-postive SLE has been evaluated in two randomized, double-blind, placebo-controlled Phase 3 studies that included a total of 1,684 patients. The two studies had a similar design and evaluated doses of 1 mg/kg and 10 mg/kg in addition to stable standard therapy. Placebo-controlled treatment continuing through Week 52 in study C1057 and through Week 76 in study C1056. A Phase 2 study (LBSL02), although supportive, does not contribute substantially to the integrated assessment of efficacy given differences in the patient population, primary efficacy endpoint and lack of SLE background medication control.

Primary efficacy evaluation in the pivotal trials for belimumab used a composite endpoint, the SLE responder index (SRI), which evaluated the response rate at Week 52. The SRI is composed of three tools as follows: ≥4 point reduction from baseline in SELENA SLEDAI score; no worsening in Physician's Global Assessment (PGA); and no new BILAG A organ domain score or 2 new BILAG B organ domain scores, as compared with baseline. These three components are widely used in clinical trials of SLE.

Although limited data are available on the minimally important clinical differences for each of these indices and the clinical relevance for the cut-off value has not been established (some authors have suggested larger reductions than ≥4 points in SELENA SLEDAI score), the proposed cut-off is overall accepted. Also, the composite endpoint (SRI) has been endorsed by CHMP in a Central Scientific Advice preceding this MAA.

Further assessment of the efficacy profile of belimumab includes numerous secondary endpoints covering SLE disease activity, flares, steroid use, and physician and patient reported outcomes. The PGA, the steroid sparing effect, and a reduction in the rates and severity of flares are considered to be of particular clinical relevance.

In study C1056, regarding mean change/percent change in PGA at Week 24, reductions (indicating improvement) were comparable across groups with no significant differences. In study C1057, belimumab 10 mg/kg was superior to placebo at Week 24 (difference=14.3%, p=<0.0001).

The effect on disease activity was accompanied by a modest CS sparing effect. The percentage of subjects whose average prednisone dose was reduced by ≥25% from baseline to ≤7.5 mg/day during Weeks 40 through 52 was only numerically higher in the 10 mg/kg group vs. placebo in both pivotal

trials. When the data were pooled, a significant difference of 5.64% was achieved as compared to placebo.

The modest benefit shown for the primary endpoint with limited support from the analyses of the secondary endpoints yielded a number of questions regarding the efficacy of belimumab. Major objections were therefore raised during the procedure comprising a number of specific questions mainly asking for alternative analyses of the Phase 3 studies.

The additional analyses requested by CHMP showed that the magnitude of effect was similar or more pronounced using a more stringent responder definition (a reduction >6 or a score <2 on the SLEDAI component). In particular, a significant difference was obtained at week 76. The observed effect was not due to improvement in immunological parameters only. Also, the imbalance with respect to the medication failure component of the responder definition did not have an impact on the results. In alternative analyses allowing different degrees of violation of the concomitant medication rules, effects consistent with the results from the analysis of the protocol-specified primary endpoint were demonstrated. The larger effect magnitude demonstrated for the primary endpoint in high disease activity subgroups (SLEDAI score >10, Positive Anti-dsDNA and low C3/C4, and Low C3/C4 and steroid requirement at baseline) was further supported by significant results for key secondary endpoints (prednisone reduction, FACIT fatigue score and time to first severe flare) in these subgroups. The responder difference at week 76 was more pronounced (10-12 percentages) in the high disease activity subgroups compared to the overall result (6 percentages).

To determine the actual effect (in terms of differences from placebo) of belimumab in the population with anti-dsDNA negative and/or normal complement levels, the Applicant was requested to present efficacy data for this subgroup which was provided during the procedure. As anticipated, the effect of belimumab 10 mg/kg in the population with NOT (anti-dsDNA positive/low complement levels), in terms of differences over placebo, was almost nil (3.8%, OR 95%CI 1.1 (0.8, 1.6)). It is noted that this population represent three different subsets of patients, i.e. antiDNA+/normal complement, antiDNA-/normal complement, antiDNA-/low complement.

In summary, the uncertainty about the robustness of the results for the primary endpoint was resolved by additional analyses and an effect was demonstrated in patients with high disease activity that was considered clinically relevant.

2.6. Clinical safety

The clinical development program for belimumab included studies in healthy volunteers and in patients with autoimmune diseases (SLE and RA). In total, 2,272 subjects have been exposed to belimumab; of those, 1,910 subjects were patients with SLE receiving intravenous belimumab.

In total, 12 clinical studies were submitted to support the safety of belimumab. Integrated safety data were presented for the 3 placebo-controlled repeat-dose studies in SLE (the Phase 2 study LBSL02 and the Phase 3 studies C1056 and C1057) (IV SLE CRD studies).

The primary safety population integrated 2,133 subjects from the 3 randomized, placebo-controlled trials completed to date with belimumab administered intravenously in patients with SLE (LBSL02, C1056 and C1057), as well as the long term data from the open-label, uncontrolled, continuation trial in subjects with SLE (LBSL99). All three randomized, controlled studies included a placebo group as well as a 1 mg/kg and 10 mg/kg belimumab dose group, respectively, each in combination with standard of care SLE therapies; LBSL02 also included a 4 mg/kg belimumab treatment arm in addition.

The secondary safety population included data from RA controlled studies, supporting data from completed Phase 1 studies, ongoing studies as well as investigator-initiated trials. Only SAEs from the ongoing IV studies in SLE are presented (C1056, LBS99, C1066, C1074) and discussed briefly. As of 31 December 2009, 233 subjects had entered Study C1066 (85 in the 1 mg/kg group and 148 in the 10 mg/kg group) and 712 subjects had entered Study C1074 (235 in the 1 mg/kg group and 477 in the 10 mg/kg group); enrollment was still continuing from the parent studies, C1056 and C1057. In total, 296 subjects had entered Study LBSL99; all were receiving 10 mg/kg.

Enrollment by Study (Sponsor-supported Studies as of 31 Dec 2009)

Belimumab Clinical Studies	Total enrolled	Total belimumab treatment
All Studies	2,578	2,272
IV SLE Studies	2,203	1,910
Primary Safety Population	2,133	1,546
Phase 2 (LBSL02, LBSL99)	449	424
Phase 3 (C1056, C1057)	1,684	1,122
C1056 (BLISS-76)	819	544
C1057 (BLISS-52)	865	578
Other Completed Studies		
Phase I (LBSL01)	70	57
Other Ongoing Studies		
C1066/C1074		307[1]
IV RA Studies (*Secondary Safety Population*)	283	270
Phase 2 (LBRA01, LBRA99)	283	270
SC Studies	92	92
Phase 1 - Healthy volunteer (C1058)	36	36
Phase 2 - SLE (C1070)	56	56

[1] Denotes number of subjects from parent studies (C1056 and C1057) who, upon enrollment in these continuation studies, switched from placebo to belimumab treatment. In total, 945 subjects from C1056 and C1057 enrolled in C1066 and C1074, as of 31 December 2009.

Patient exposure

In total, 2,578 subjects participated in the belimumab clinical development program. Of the 2,133 subjects in the primary safety population approximately 70% received at least 12 months of blinded treatment with belimumab; the mean number of doses received was 13 in each treatment group.

The duration of exposure for all controlled and uncontrolled IV SLE studies is summarized in the table below.

Duration of Exposure - All IV SLE Studies

	Placebo N=688	1 mg/kg N=688	4 mg/kg N=125	10 mg/kg[2] N=946	20 mg/kg N=14	All Active N=1603[3]
Duration of exposure[1] (days)						
Mean ± SD	346.72 ± 123.34	358.78 ± 130.80	358.27 ± 164.84	619.83 ± 495.46	38.36 ± 10.76	548.05 ± 486.55
Median	368.0	370.0	393.0	392.0	38.0	371.0
(Min, Max)	(28.0, 553.0)	(28.0, 625.0)	(28.0, 589.0)	(28.0, 1933.0)	(28.0, 50.0)	(28.0, 1937.0)
Duration of exposure[1] (months)						
≥3	636 (92.4%)	637 (92.6%)	106 (84.8%)	876 (92.6%)	--	1463 (91.3%)
≥6	598 (86.9%)	604 (87.8%)	102 (81.6%)	828 (87.5%)	--	1386 (86.5%)
≥ 9	544 (79.1%)	566 (82.3%)	99 (79.2%)	779 (82.3%)	--	1302 (81.2%)
≥12	458 (66.6%)	473 (68.8%)	93 (74.4%)	677 (71.6%)	--	1107 (69.1%)
≥18	1 (0.1%)	20 (2.9%)	23 (18.4%)	271 (28.6%)	--	297 (18.5%)
≥24[3]	--	--	--	257 (27.2%)	--	274 (17.1%)
≥30[3]	--	--	--	242 (25.6%)	--	257 (16.0%)
≥36[3]	--	--	--	226 (23.9%)	--	248 (15.5%)
≥42[3]	--	--	--	181 (19.1%)	--	229 (14.3%)
≥48[3]	--	--	--	73 (7.7%)	--	175 (10.9%)
≥54[3]	--	--	--	53 (5.6%)	--	151 (9.4%)
≥60[3]	--	--	--	16 (1.7%)	--	38 (2.4%)

Studies LBSL01, LBSL02, LBSL99, C1057 and C1056.

1 Duration is calculated as last infusion date - first infusion date + 28 days. A 3 month interval is defined as 13 weeks.

2 Includes subjects randomized to the 10 mg/kg group and subjects who switched to the 10 mg/kg group. For subjects who switched to the 10 mg/kg group, exposure was calculated after their 1st dose of 10 mg/kg belimumab treatment.

3 In the "10 mg/kg" column: Only the exposure to belimumab 10 mg/kg treatment was counted. In the "All Active" column": For patients who switched to belimumab 10 mg/kg group from belimumab 1 mg/kg or 4 mg/kg groups, the initial exposure to belimumab 1 mg/kg or 4 mg/kg treatment was counted in addition to the exposure to belimumab 10 mg/kg treatment.

Approximately 15% to 25% of subjects discontinued during the blinded treatment phase, across the belimumab and placebo treatment groups with no trends in relation to dose.

Adverse events

Common AEs

The overall incidence of treatment-emergent AEs for the combined studies LBSL02, C1056, and C1057 (IV SLE CRD studies=primary safety population) is summarized in the table below.

Number of Subjects with AEs (IV SLE CRD Studies)

	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
At least 1 AE	624 (92.4%)	626 (93.0%)	107 (96.4%)	625 (92.7%)
At least 1 related[1] AE	285 (42.2%)	270 (40.1%)	53 (47.7%)	269 (39.9%)
At least 1 serious AE	107 (15.9%)	125 (18.6%)	15 (13.5%)	117 (17.4%)
At least 1 severe[2] AE	104 (15.4%)	104 (15.5%)	26 (23.4%)	103 (15.3%)
At least 1 related serious AE	34 (5.0%)	35 (5.2%)	1 (0.9%)	31 (4.6%)
At least 1 related severe[2] AE	28 (4.1%)	28 (4.2%)	5 (4.5%)	25 (3.7%)
At least 1 AE resulting in dosing interruption	85 (12.6%)	86 (12.8%)	25 (22.5%)	91 (13.5%)
At least 1 AE resulting in study agent discontinuation	48 (7.1%)	42 (6.2%)	4 (3.6%)	45 (6.7%)
Deaths	3 (0.4%)	5 (0.7%)	--	6 (0.9%)

Studies LBSL02, C1056, and C1057
[1] Related is defined as possibly, probably or definitely related to study agent.
[2] Severe refers to Grade 3 and Grade 4.
Source: Summary of Clinical Safety.

The incidence of treatment-emergent AEs was generally fairly similar across the 1 mg/kg, 10 mg/kg, and placebo groups. The most common AEs are summarized in the table below.

Reviewed by MedDRA system organ class (SOC), the incidence of subjects with AEs was generally similar in the belimumab 1 mg/kg and 10 mg/kg groups compared with the placebo group. The highest incidence of AEs occurred in the Infections and Infestations SOC and slightly more frequently so in the belimumab 1 mg/kg (71.0%) and 10 mg/kg groups (69.9%) compared with placebo (66.7%). Psychiatric Disorders (15.3% in the 1 mg/kg group, 14.8% in the 10 mg/kg group vs. 12.1% for placebo), Eye Disorders (10.4% and 10.8% vs. 8.7%, respectively), and Cardiac Disorders (6.5% and 8.2% vs. 6.7%, respectively) were also reported at slightly higher incidences in the belimumab groups versus placebo.

Common AE preferred terms that were reported slightly more frequently in the belimumab groups compared with placebo included: nausea (14.7% in the 10 mg/kg groups and 13.1% in the 1 mg/kg group vs. 12.1% in the placebo group); diarrhoea (12% in both belimumab groups compared with 9.2% in the placebo group); nasopharyngitis (9.1% in the 10 mg/kg and 8.5% in the 1 mg/kg group vs. 7.1% for placebo); bronchitis (8.9% in the 10 mg/kg and 6.4% in the 1 mg/kg group vs. 5.2% for placebo); pain in extremity (5.9% and 5.2% vs. 4.0%) ; and depression (5.2% and 6.1% vs. 3.7%).

Other events that were more commonly reported in the 10 mg/kg belimumab group compared with placebo included leukopenia, pyrexia, cystitis, viral gastroenteritis, migraine, and insomnia. However, the difference in incidence between the treatment groups for these common events was small.

In the IV SLE CRD studies, 2.1% of subjects in the 10 mg/kg belimumab group had an AE coded as 'infusion-related reaction' compared with 1.3% in the 1 mg/kg group and 0.7% of subjects treated with placebo (see 'adverse events of special interest').

Of note, the overall incidence of AEs reported in the 4 mg/kg group was higher than in the 1 mg/kg and 10 mg/kg belimumab groups. This is caused by the fact that the incidence of AEs and laboratory abnormalities was higher in Study LBSL02 across all treatment groups, including the placebo group, as compared with the Phase 3 studies. The reason for this is not known, possibly a combination of various factors such as differences in the number of study visits or possibly some differences in age, disease duration or geographic distribution between the study populations.

Most Common AEs (>10% in the 10 mg/kg Group) (IV SLE CRD Studies)

Preferred Term	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
Headache	140 (20.7%)	138 (20.5%)	30 (27.0%)	142 (21.1%)
Upper respiratory tract infection	130 (19.3%)	128 (19.0%)	36 (32.4%)	118 (17.5%)
Arthralgia	112 (16.6%)	100 (14.9%)	32 (28.8%)	109 (16.2%)
Nausea	82 (12.1%)	88 (13.1%)	22 (19.8%)	99 (14.7%)
Urinary tract infection	82 (12.1%)	92 (13.7%)	19 (17.1%)	87 (12.9%)
Diarrhoea	62 (9.2%)	81 (12.0%)	23 (20.7%)	80 (11.9%)
Fatigue	70 (10.4%)	71 (10.5%)	33 (29.7%)	66 (9.8%)
Pyrexia	52 (7.7%)	52 (7.7%)	17 (15.3%)	65 (9.6%)

Studies LBSL02, C1056, and C1057

Most AEs in the IV SLE CRD studies were mild to moderate in severity. Severe AEs (Grade 3 or Grade 4) were reported for approximately 15% of subjects in the 1 mg/kg and 10 mg/kg groups, as well as the placebo group. There were no major differences in the distribution of severe events between the treatment groups. However, slightly more subjects treated with the 10 mg/kg belimumab dose experienced severe events of pyrexia, leukopenia, myalgia, and infusion related reactions compared with placebo.

To determine whether AEs were related to duration of exposure to study agent, the incidence of subjects with AEs was calculated for 6-months intervals for the controlled IV SLE CRD studies. The rate of subjects with at least 1 AE, related AE, serious AE, and severe AE per 100-subject years was somewhat higher during the first 6-month interval compared with the second 6-month interval. Similarly, the AE profile over a prolonged period of time was further assessed in the repeat-dose long-term LBSL02 extension and LBSL99, showing that the rates for most AEs tended to decline with time. Also, there was no clear indication of an increase in the incidence of severe AEs with increasing duration of exposure to study agent over the course of the studies.

In the IV SLE CRD population (C1056, C1057 and LBSL02) 83% of the total population were on any steroids at baseline. The table below displays the frequency of patients who experienced infusion reactions, hypersensitivity reactions, infections and serious infections by the use of steroids at baseline. Interpretation of these results should be made with caution given the relatively small number of patients not on steroids.

Table Patients who experienced an AE by baseline steroid use. IV SLE CRD population

	On Steroids at baseline (N = 1686)			No Steroids at baseline (N = 336)		
	Placebo (n = 570)	1 mg/kg (n = 565)	10 mg/kg (n = 551)	Placebo (n = 105)	1 mg/kg (n = 108)	10 mg/kg (n = 123)
Infusion reactions/hypersensitivity	30 (5.3%)	33 (5.8%)	47 (8.5%)	8 (7.6%)	19 (17.6%)	15 (12.2%)
Hypersensitivity reactions	1 (0.2%)	2 (0.4%)	2 (0.4%)	0	1 (0.9%)	0

Infections	378 (66.3%)	401 (71.0%)	380 (69.0%)	72 (68.6%)	77 (71.3%)	91 (74.0%)
Serious Infections	33 (5.8%)	39 (6.9%)	31 (5.6%)	2 (1.9%)	7 (6.5%)	4 (3.3%)

Table 20.01-Table 20.06 m5.3.5.3

Overall, the proportion of subjects with infusion reactions was lower in the population on steroids in all treatment groups; the greatest proportion of subjects with events was observed in the 10 mg/kg belimumab group. Hypersensitivity reactions, however, do not appear to be significantly decreased on steroids although the numbers are small and so a definitive conclusion with regards to hypersensitivity reactions cannot be made. It should be noted that all the cases of anaphylaxis and angioedema occurred in the group on steroids.

Rates of patients experiencing any infection did not increase in patients on steroids, which is somewhat surprising. The difference in rates between the 10 mg/kg and the placebo group was increased slightly (2.7% difference in subjects on steroids, 5.4% difference in subjects not on steroids). Serious infection rates on the other hand were greater in all treatment groups on steroids, and therefore steroids may play a more critical role in the development of serious infections than does belimumab.

Adverse events of special interest

- Infusion and hypersensitivity reactions

As an AE of special interest, the Applicant conducted an analysis of infusion reactions (including hypersensitivity reactions) that occurred. For the purpose of this analysis, 'infusion reactions' were defined as all events that were included in list of 164 preferred terms and that had a duration ≤7 days. In addition, nine preferred terms related to 'hypersensitivity reaction' did not have this duration requirement and were also considered infusion reactions.

The majority of reactions occurred with either the first or second infusion and the incidence declined with subsequent infusions. The difference in incidence of events between the 10 mg/kg group vs. placebo was most apparent during the first few infusions and reduced over time. One of the reasons may be that subjects with severe or serious reactions were discontinued but there were also fewer reports over time in the placebo group.

Fifteen subjects in the IV SLE CRD studies had serious infusion or hypersensitivity reactions: 3 (0.4%) in the placebo group and 6 (0.9%) each in the 1 mg/kg and 10 mg/kg groups. Infusion-related reaction (not specified) was the most commonly reported SAE preferred term: 2 (0.3%), 1 (0.1%), and 4 (0.6%) subjects in the placebo, 1 and 10 mg/kg groups, respectively. Specific symptoms of events reported as serious infusion-related reactions were variable.

Overall, the data indicate that the incidence of infusion reactions and hypersensitivity reactions were greatest during the first few infusions but in some cases, the reactions occurred later. The incidence of serious reactions was approximately 1% both for the 1 mg/kg and the 10 mg/kg dose.

Recommendations for considering premedication and cautionary language have been included in the SPC.

- Infections

Based on the mechanism of action of belimumab, the risk of infection is a potential concern. In the randomized controlled SLE trials, the overall incidence of infections was 67% in the placebo group, 71% in the 1 mg/kg group, and 70% in the 10 mg/kg group. The most frequent infections by preferred term were upper respiratory tract infection, urinary tract infection, nasopharyngitis, sinusitis and bronchitis. The incidence of these events was generally comparable between all groups, with the exception of bronchitis and nasopharyngitis, which were slightly more common in the belimumab groups.

Severe infections occurred in from 3% to 5% of subjects across the treatment groups (3.7%, 3.9% and 3.3% in the placebo, belimumab 1 mg/kg and 10 mg/kg groups, respectively).

The incidence of the most frequent serious infections is shown in the table below, showing a similar incidence except for bronchitis which occurred slightly more frequently in subjects treated with belimumab. In addition, the incidence of sepsis was slightly higher for belimumab compared with placebo (0.7% for the 10 mg/kg group compared with 0.4% for placebo). There were 5 SAEs of sepsis (0.7% of subjects) in the belimumab 10 mg/kg group compared with 1 subject (0.1%) in the placebo group.

Most Frequent Serious Infections by Preferred Term (IV SLE CRD Studies)

System Organ Class Preferred Term [1]	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
Serious Infections and infestations	35 (5.2%)	46 (6.8%)	7 (6.3%)	35 (5.2%)
Pneumonia	10 (1.5%)	7 (1.0%)	1 (0.9%)	6 (0.9%)
Urinary tract infection	4 (0.6%)	7 (1.0%)	1 (0.9%)	5 (0.7%)
Cellulitis	2 (0.3%)	7 (1.0%)	1 (0.9%)	1 (0.1%)
Bronchitis	1 (0.1%)	2 (0.3%)	1 (0.9%)	3 (0.4%)
Pyelonephritis	3 (0.4%)	3 (0.4%)	--	--

Studies LBSL02, C1056, C1057
[1] Preferred terms are sorted by descending frequency across all treatment groups.

Two deaths were specifically attributed to sepsis - one subject in the 1 mg/kg group and one subject in the 10 mg/kg group of Study C1057, while a third subject in the placebo group in this study died of cardiac arrest that was preceded by sepsis. In addition, another death in the 10 mg/kg group was attributed to active infective diarrhoea. Two deaths occurred from respiratory failure (Study LBSL02, 10 mg/kg group) or respiratory arrest (Study C1057, 1 mg/kg group) with sepsis also noted among other events experienced by the subjects. An additional death in the 1 mg/kg group (Study C1056) was of unknown causation but was considered related to vomiting following an unspecified gastrointestinal illness.

Thus, the number of deaths with relation to sepsis in the controlled studies was slightly higher in the belimumab groups, compared with placebo. However, a possible relationship to belimumab is not always clear. In addition, there were a few cases of serious opportunistic infection (including one subject with disseminated CMV infection (on Day 62) and one subject with Acinetobacter bacterimia, on Day 15) both in the 10 mg/kg group and a possible relationship to belimumab cannot be excluded.

The anti-TNF activity of belimumab is an area of concern with respect to infection risk. BLyS is a member of the tumour necrosis factor ligand superfamily. It has been shown to bind with high affinity to 3 receptors, all of which are members of the TNF receptor family (BCMA, TACI, and BAFF-R).

The Applicant conducted a separate analysis that included infection AEs of special interest: cellulitis, fungal infections, herpes infections, sepsis, all respiratory infections, and possible opportunistic

infections. All but fungal/herpes viral infections were reported in a slightly greater proportion of belimumab subjects than placebo subjects.

The Applicant was also requested to further discuss the potential risk of opportunistic infections such as tuberculosis in countries with a higher prevalence of latent tuberculosis. A summary of the incidence of opportunistic infections as of 09 July 2010 is shown in the table below.

Opportunistic infection rate in all belimumab SLE studies as of 09 July 2010

	Belimumab Studies			
	IV SLE CRD		All SLE Studies	
	Placebo	All Active	Placebo	All Active
No. Patients	675	1458	688	1982
Patient years	692	1516	702	3,976
Opportunistic Infections	0	3[1]	0	9[1,2]
Opportunistic infection rate / 100 patient years	0	0.20	0	0.23
95% Confidence Interval	(0.00, 0.43)	(0.04, 0.56)	(0.00, 0.43)	(0.10, 0.43)

Source: Table TA194 and TA195, m5.3.5.3
1 Includes one event reported on Day 0 and therefore unlikely to be related to belimumab.
2 Includes 4 events reported in the MAA (3 in the primary safety population and 2 in LBSL99) and an additional 5 events reported through 09July2010 in long-term continuation studies.

As of 09 July 2010, three cases of TB (two pulmonary [latent] TB, one extra pulmonary TB) have been reported in long-term SLE studies. Two of these cases were considered serious and one non-serious. The two serious cases occurred in subjects in the Philippines and Taiwan; the third, non-serious case occurred in a US subject originally from Cambodia. All belimumab-treated subjects that experienced TB were taking steroids and two were additionally taking an immunosuppressant (azathioprine or mycophenolate mofetil). An additional case of non-serious latent TB was identified in a SLE long-term continuation study, plus two non-serious cases of non-tuberculosis mycobacterial infections.

The Applicant also conducted an analysis of infection risk in relation to the incidence of Grade 3 or 4 laboratory abnormalities in white blood cells and immunoglobulins. These data seem to indicate a higher risk of infection in subjects treated with belimumab and with Grade 3 or 4 lymphopenia or low immunoglobulin level; however, the results should be interpreted with caution. Temporal relationships between onset of infection and laboratory measures were not established and the submission of some additional controlled Week 76 data (Study C1056) did not provide significant new information.

As a component of the RMP, the Applicant is proposing to conduct a large post-marketing safety study to evaluate the long-term safety of IV belimumab in the SLE population by assessment of the incidence of serious infections as well as opportunistic infections for at least 5 years.

- Malignancies

As an immunomodulator, a possible concern with belimumab is the potential risk for malignancy.

During the double-blind period of the IV SLE CRD studies, a total of 8 subjects had malignant neoplasms (two in the placebo group and three each in the 1 mg/kg and 10 mg/kg group), and one subject had a neoplasm for which the malignancy status was not specified (thyroid neoplasm). An additional malignant neoplasm was reported for one subject (breast cancer, placebo group) poststudy. Of these 10 neoplasms, six were solid organ neoplasms and four were non-melanoma skin neoplasms. No haematological neoplasms were reported in these studies.

Overall, the IV SLE CRD studies showed a comparable incidence of malignancy between belimumab and placebo over a relatively short observation period and no particular trends were observed.

An up-to-date malignancy incidence estimate for all SLE studies as of 09 July 2010 is shown in the table below, which similarly did not show a particular trend. Similarly, an update on the rate of haematological malignancies across all SLE studies was estimated at 0.075/100 subject-years (95% CI: 0.016, 0.221), compared with a background rate for SLE patients at 0.087 (0.067, 0.111) as reported in the literature.

As a component of the RMP, the Applicant is proposing a post-marketing randomized , controlled l study to collect additional malignancy data over a period of at least 5 years.

Malignancy rate excluding NMSC in all belimumab SLE studies as of 09 July 2010

	Background Rate	Belimumab Studies			
		IV SLE CRD[1]		All SLE Studies[2]	
	Bernatsky et al, 2005	Placebo	All Active	Placebo	All Active
No. Patients	9547	675	1458	688	1,982
Patient years	76,948	692	1516	702	3,976
All malignancies	410	2	3	2	18
Malignancy rate / 100 subject years	0.53	0.29	0.20	0.28	0.45
95% Confidence interval	(0.48, 0.59)	(0.04, 1.04)	(0.04, 0.58)	(0.03, 1.03)	(0.27, 0.72)
Hematological malignancies	67	0	0	0	3
Hematological malignancy rate / 100 subject years	0.087	0.000	0.000	0.000	0.075
95% Confidence interval	(0.067, 0.111)	NP[4]	NP[4]	(0.000, 0.427)	(0.016, 0.221)

1. Includes Studies LBSL02, C1056, and C1057 as updated and reported in 120-Day Safety Update
2. Includes Studies LBSL01, LBSL02, C1056, C1066, C1074, C1070, and LBSL99 as updated and reported in the 120-day Safety Update. Note that placebo subjects were followed for up to 18 months while belimumab subjects were followed for up to 5 years.
3. Includes b cell lymphoma (n=2) and multiple myeloma (n=1)
4. Not provided

- Other events of special interest

Additional exploratory AE analyses by the Applicant included psychiatric disorders, eye disorders, cardiovascular disorders and gastrointestinal infections.

Psychiatric disorders

Neuropsychiatric events such as major depressive disorder, bipolar disorder, panic disorder are known to be significantly higher in patients with SLE than in the general population. In the IV SLE CRD studies, slightly higher rates of psychiatric disorders were seen in the belimumab groups compared to placebo (15% vs. 12%), which seemed mostly driven by depression, anxiety and insomnia. The incidence of composite depression and suicide/self injury AE preferred terms was slightly higher in the belimumab groups (namely 4.7%, 6.4%, and 5.5% in the placebo, 1mg/kg, and 10 mg/kg groups, respectively).

Across all controlled and uncontrolled SLE studies, there were three reports of completed suicide and one report each of suicide attempt and suicidal gesture in the belimumab groups, compared with one report of intentional self-harm in the placebo group. In most cases there was a history of depression. Further, incidence rates for serious depression or related events in SLE studies were lower than those reported in the literature for patients with SLE and similar in the case of suicidal behaviour.

The Applicant was requested to further discuss this issue and concluded that the belimumab studies showed a slight increased incidence in neuropsychiatric disorders for belimumab compared with placebo, mainly driven by reports of depression. The reason for this slight difference is not clear and could not be explained by imbalances in medication at baseline since the proportions of subjects receiving concomitant medications for depression and suicide/self-injury were similar across treatment groups. However, in the 10 mg/kg a slightly greater proportion of subjects reported medical history of depression and suicide/self-injury at baseline which may be an indication that there was a slightly greater predisposition for the development or worsening of depression than in the other treatment groups. Psychiatric events including depression and suicidality are included in the RMP as a potential risk. The Applicant will prospectively evaluate data on psychiatric events, including depression and suicidality, reported from ongoing and other future clinical studies, including the planned 5-year randomized, controlled study.

Eye disorders

Slightly more eye events were noted in the belimumab groups (10% and 11% in the 1 mg/kg and 10 mg/kg groups, respectively) compared with placebo (8.7%). However, no specific event was responsible for the difference observed, and the most frequent events were relatively minor disorders (e.g., dry eye).

Cardiovascular disorders

A higher reporting of cardiac disorders SOC in belimumab groups compared to placebo was seen in Study C1056 but not Study C1057. In Study C1056, the rate of cardiac disorders was 5.5%, 8.9%, and 11% for placebo, 1 mg/kg, and 10 mg/kg, respectively, and palpitations was the most common preferred term (1.5%, 1.8% and 2.6% in the placebo, belimumab 1 mg/kg and 10 mg/kg groups, respectively).

Overall, in the IV SLE CRD studies cardiac arrhythmias were slightly more commonly reported in the belimumab groups compared to placebo, with an incidence of 3.6% in the 1 mg/kg group and 4.6% in the belimumab 10 mg/kg group compared with 3.0% for placebo. This was mainly driven by non-serious palpitations but could not be explained by infusion-related events.

Gastrointestinal infections

An increase in the incidence of GI infections might be expected following belimumab treatment (1.0%, 3.4%, and 3.3% for placebo and belimumab 1 and 10mg/kg, respectively). In most cases, these were nonserious AEs.

Serious adverse event and deaths

Deaths

Prior to 01 January 2010, 28 deaths had been reported across the entire belimumab clinical development program with two additional deaths reported in long-term safety studies of belimumab in the interval from 01 January to 09 July 2010.

Fourteen deaths occurred during the double-blind periods of the IV SLE CRD studies: 3 (0.4%) in the placebo group, 5 (0.7%) in the 1 mg/kg group and 6 (0.9%) in the 10 mg/kg group. Nine of the deaths occurred in Study C1057 compared with three in Study C1056 and two in Study LBSL02. Eight of the deaths occurred during first 6-month interval and six deaths occurred during the second 6-month interval. An additional death due to respiratory arrest was reported more than 3 months after the subject completed participation in Study C1057 (1 mg/kg group). Of these 15 deaths, three were due to cardiac disorders, three due to infections and infestations, three due to respiratory failure/arrest, two due to suicide, two due to unknown cause, one due to ischemic stroke, and one due to ovarian cancer.

Three deaths were reported in open-label long-term SLE study LBSL99 prior to the cut-off date for the interim CSR: suicide, CMV pneumonia, and atherosclerotic coronary artery disease. Two deaths were reported in the controlled RA study LBRA01 (myocardial infarction, pneumonia) and two deaths were reported in the open-label long-term study LBRA99 (coronary artery thrombosis, respiratory failure).

Eight additional deaths were reported in the ongoing studies in SLE and RA.

Although the death rate in the controlled studies was more than twice as high in the 10 mg/kg group compared with the placebo group (0.9% vs. 0.4%), review of individual cases was not indicative of particular trends for belimumab. In most cases, the cause of death could be related to severe SLE and subsequent complications, and other underlying conditions. However, for some of the subjects who died from infection, a contributory role by belimumab cannot be excluded.

An updated death incidence rate across all SLE studies is shown in the table below. Including the two deaths reported since 01 January 2010 and adjusting for exposure to 09 July 2010, the death incidence rate per 100 patient-years is 0.43 in placebo-treated patients (95% CI: 0.09, 1.25) and 0.55 in belimumab-treated patients (95% CI: 0.35, 0.84).

Mortality rate in all SLE studies as of 09 July 2010

	Background Rate	All SLE Studies[1]	
	Bernatsky et al, 2006	Placebo	All Active
No. Subjects	9,547	688	1,982
Subject years[2]	76,948	702	3,976
Deaths	1,255	3	22
Death rate / 100 subject years	1.63	0.43	0.55
95% Confidence interval	(1.54, 1.72)	(0.09, 1.25)	(0.35, 0.84)

[1] Includes LBSL01, LBSL02, LBSL99, C1056, C1057, C1066, C1074, and C1070.

SAEs

Overall, the incidence of SAEs in the IV SLE CRD studies was high and similarly distributed across the treatment groups, including placebo (17% in the 10 mg/kg, 19% in the 1 mg/kg, and 16% in the placebo group). These rates are not unexpected for a moderately severe active SLE disease population. The most frequent SAEs were pneumonia, pyrexia, and urinary tract infection. There were relatively more cases of serious pyrexia and depression in the belimumab groups and relatively more cases of non-cardiac chest pain in the placebo group but the absolute number of events was small.

The Applicant was requested to further discuss the observation that the incidence of severe and/or serious nervous system disorders and renal disorders appeared to be higher in the belimumab groups compared to placebo. During the procedure the Applicant provided additional analyses of the incidence of SAEs and severe adverse events with respect to renal disorders (Renal and Urinary Disorders SOC) and nervous system disorders (Nervous System Disorders SOC) in the IV SLE CRD studies. These analyses did not reveal trends or findings that indicated a causal relationship to belimumab. Many events were single reports and did not comprise a particular pattern.

Seven cases of pancreatitis were reported in patients on belimumab, two in belimumab 4 mg/kg and five in belimumab 10 mg/kg. In 4 out of 7, the potential role of belimumab could not be ruled out. However, the calculated pancreatitis rate/100 patient years was higher in the placebo group (0.71/100 patient years) compared to belimumab across all dose groups (0.18/100 patient years); furthermore, a higher incidence of pancreatitis among placebo patients (0.7%) compared to subjects receiving belimumab 10 mg/kg (0.3%) was observed.

In general, most SAEs were considered not related to study drug. The SOC with the highest incidence of related SAEs was 'Infections and infestations'. The most frequently reported (≥5 subjects in total) related SAEs within this SOC were pneumonia, UTI, cellulitis, and herpes zoster with no notable differences between the treatment groups. The next highest incidence of related SAEs reported was in the 'General disorders' and 'Administration site condition' SOC, with infusion-related reactions being most prevalent.

More subjects treated with belimumab developed SAEs of infusion related reaction or hypersensitivity reaction compared with placebo. Four subjects (0.6%) in the 10 mg/kg belimumab group experienced SAEs of 'infusion related reaction' combined with 2 subjects (0.3%) in the 1 mg/kg group and 2 (0.3%) in the placebo group. In addition, 2 (0.3%) subjects in the 10 mg/kg and 2 (0.3%) subjects in the 1 mg/kg group had SAEs coded as anaphylactic reaction or drug hypersensitivity reaction, compared with none in the placebo group. Two of the subjects with an anaphylactic reaction also developed angioedema. All events were considered at least possibly related to study drug.

Laboratory findings

Most of the hematology, clinical chemistry and urinalysis values were similar between the placebo and the belimumab groups. Lymphopenia was the most common laboratory abnormality, which also had a similar distribution across the groups. Twenty-three percent, 26% and 24% of subjects in the placebo, 1 mg/kg and 10 mg/kg groups, respectively, experienced a Grade 3 lymphopenia during the study and 2.8%, 1.8% and 3.0%, respectively, experienced Grade 4.

The effects of belimumab could be seen more clearly in B cell subsets, which were assessed in Study C1056. Treatment with belimumab reduced selected B cell subsets such as CD19+ B cells, and naïve (CD20+/CD27-) and activated (CD20+/CD69+) B cells, plasma cells, short lived plasma cells, and the SLE subset of B cells (active B cell subsets associated with SLE disease activity), whereas memory B

cell compartment and T cells were preserved. In Study C1056, belimumab significantly reduced both CD19+ and CD20+ B cells compared with placebo continuously through Week 76.

At Week 76, the median percent reduction in CD19+ cells with belimumab was 56-58% compared with 3% with placebo. The median reduction in naïve B cells in subjects treated with belimumab at Week 76 was 73%-76% compared with 3% for placebo. The median reduction in activated B cells was 25%, 43%, and 49% with placebo, 1 mg/kg and 10 mg/kg belimumab, respectively.

To date, B-cell subset data with ongoing treatment beyond Week 76 are not available and it is not clear whether the decline in B cell subsets eventually stabilizes with ongoing treatment. However, B-cell subsets are being collected in the ongoing Phase 3 continuation study, C1066. At the time of the analysis, subjects treated with belimumab since randomization will have at least 3 years of B-cell data and subjects who switched from placebo to belimumab in the continuation study will have at least 1.5 years of data.

Reduction of immunoglobulins (IgG, IgA, and IgM) is also an expected pharmacologic effect of belimumab. At Week 52 of treatment in the Phase 3 SLE studies (C1056 and C1057), the median percent change from baseline in IgG was -2.5%, -14%, and -15%, in the placebo, 1 mg/kg, and 10 mg/kg groups, respectively. However, most subjects had IgG values that remained within the reference range at each visit.

The incidence of IgM shifts from high/normal at baseline to below LLN was higher in the belimumab groups (17%, 21%, and 19% for 1, 4, and 10 mg/kg, respectively) compared with the placebo group (6.0%). The median percent change from baseline to Week 52 in IgM was 1.3%, -28%, and -30%, respectively.

IgA shifts from high/normal to low were infrequent, but also tended to occur in more subjects in the belimumab groups (2.0% to 3.7%) than the placebo group (1.2%).The median change in IgA from baseline in the belimumab groups was similar to that observed for IgG, -16% to -17%.

The association of infections, serious infections and severe infections with Grade 3 or 4 lymphopenia ($<1000/mm^3$), neutropenia ($<500/mm^3$), decreases in immunoglobulins (IgG, IgM and IgA) and decreases in T-cells was examined by the Applicant. Overall, there were no significant changes in rate of Grade 3 or Grade 4 lymphopenia, neutropenia and IgG events between placebo versus the belimumab 1 mg/kg or 10 mg/kg groups in the controlled SLE studies. However, subjects in belimumab groups who experienced Grade 3 or Grade 4 lymphopenia, neutropenia, or low IgM or IgG exhibited slightly higher rates of infections versus placebo and versus subjects without these abnormalities (see section on infections as AE of special interest).

Long-term changes in immunoglobulin levels have been reported in the uncontrolled Phase 2 continuation study LBSL99, out to 5 years:

- IgG: Among belimumab subjects with IgG ≥LLN at baseline, the proportion with IgG <LLN oscillated but generally increased gradually from 2% at Week 8 to 4% at Week 128 (2.5 years). It remained relatively stable at 4% between Week 128 out to Week 248 (5 years).
- IgM: Among belimumab subjects with IgM ≥LLN at baseline, the proportion with IgM <LLN increased consistently over time from 20% during the first year to 45% between years 4 and 5.
- IgA: Among subjects with IgA ≥LLN at baseline, the proportion of subjects with IgA <LLN increased slightly over time, from 4% during the first year to 6% between years 4 and 5.

Long-term immunosuppression may also raise the potential risk for progressive multifocal leukoencephalopathy (PML). Cases of PML have been reported for other immunosuppressives, including

compounds that target B cells, such as rituximab. To date, there have been no reports of PML in the belimumab program and to assess this risk requires a long-term follow up.

Safety in special populations

Renal elimination is not important for belimumab. Thus, the Applicant's proposal not to recommend dose adjustment for renally impaired patients is considered reasonable. The Applicant was requested to further analyze the safety data by severity of renal impairment, which did not suggest an altered safety profile under these circumstances. The Applicant recommends caution in patients with severe renal impairment due to the lack of data. This is agreed with and a statement has been added in the SPC.

IgG1 molecules such as belimumab are metabolized by ubiquitous proteolytic enzymes that are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of belimumab. No dose adjustments are recommended, which is acceptable for CHMP.

The safety of belimumab (overall incidence of AEs, as well as incidence of infections, and infusion and hypersensitivity reactions) was evaluated in various subpopulations of the IV SLE CRD studies. The intrinsic factors subject to review included the following: gender, age, race, baseline proteinuria level (≥2 gram/24hr vs. <2 gram/24 hr), and baseline SELENA SLEDAI score (≥10 vs. ≤9). In addition, the following extrinsic factors were examined: geographic region, baseline prednisone use (≤7.5 mg/day vs. >7.5 mg/day), and baseline immunosuppressant use (Yes/No).

Overall, no major trends for the difference between belimumab and placebo were observed for the subgroups. Given the low number of males or subjects >65 years of age enrolled in the studies, no meaningful gender or age subgroup comparisons could be performed. Similarly, the data on elderly was very limited.

Immunological events

In the two Phase 3 IV SLE studies, samples for immunogenicity assessment were drawn on Day 0 and at Weeks 8, 24, 52/Exit (Study C1057) and Week 76/Exit (Study C1056), as well as the 8-week follow-up (for subjects discontinuing treatment and not entering the extension period of the study). For subjects who had a positive anti-belimumab antibody response at the 8-week follow-up, an additional serum sample was obtained, if possible, at least 6 months after the last dose of study agent or upon completion and/or unblinding of the study, whichever was later. A summary of the findings is presented in the table below.

Summary of Immunogenicity (Anti-belimumab Antibodies) (Phase 3 IV SLE Studies)

	Placebo N=562	**1 mg/kg N=559**	**10 mg/kg N=563**
Persistent Positive[1]	10 (1.8%)	27 (4.8%)	4 (0.7%)
NA/Negative --> positive	10 (1.8%)	26 (4.7%)	4 (0.7%)
Positive --> positive	--	1 (0.2%)	--
Neutralizing any time post baseline[2]	7/ 10	3/ 11	0/ 1
Transient Positive[3]	1 (0.2%)	46 (8.2%)	1 (0.2%)
NA/Negative --> positive	1 (0.2%)	44 (7.9%)	1 (0.2%)
Positive --> negative	--	2 (0.4%)	--

Summary of Immunogenicity (Anti-belimumab Antibodies) (Phase 3 IV SLE Studies)

	Placebo N=562	1 mg/kg N=559	10 mg/kg N=563
Neutralizing any time post baseline[2]	--	1/ 11	--
Negative	551 (98.0%)	486 (86.9%)	558 (99.1%)

[1] Persistent positive refers to positive immunogenic response at 2 or more assessments or at the final assessment.
[2] Neutralizing any time post-baseline among subjects with neutralization assay results available.
[3] Transient positive refers to positive immunogenic response at only 1 assessment and negative at final.

Few subjects tested positive for anti-belimumab antibodies and the Applicant explained that immunogenicity detected in placebo subjects may be attributed to isolated dosing errors, sample labelling errors and/or to the expected false positive rate (<1%) observed in the absence of drug in this type of assay.

The relationship between antibody formation and the risk of infusion reactions does not appear to be strong. Of the 76, 88, and 84 Phase 3 subjects in the placebo, 1 mg/kg and 10 mg/kg groups, respectively, who experienced some type of infusion reaction or hypersensitivity reaction, four subjects (one in the placebo group, two in the 1 mg/kg group, and one in the 10 mg/kg group) also had persistent positive immune responses to belimumab. In addition, 8 subjects in the 1 mg/kg group who had an infusion or hypersensitivity reaction had transient immune responses to belimumab. However, the immunogenicity assay used had decreased sensitivity for anti-belimumab (drug) antibodies (ADA) with increased doses of belimumab. Thus, the presence of ADA in subjects in the 10 mg/kg group may be underestimated.

Safety related to pregnancy

As of 31 October 2010, 60 pregnancies were reported in the IV SLE studies, with outcome reported in 49 cases. No pregnancies were reported in the RA or Phase 1 studies. In addition, one subject in the belimumab SC SLE Study C1070 (100 mg q2 week group) became pregnant and electively terminated the pregnancy. Overall, the data is too limited to conclude whether the rate of adverse outcomes in pregnant subjects who receive belimumab is similar to the general population with SLE.

The RMP includes a pregnancy registry to collect more information on pregnancy outcome. The importance of obtaining further information of belimumab treatment during pregnancy was also emphasized by the experts convened in the Ad hoc expert group meeting.

Safety related to drug-drug interactions and other interactions

Belimumab is not metabolized by the cytochrome P450 system. No studies with belimumab have been conducted to specifically examine drug-drug interactions. However, the Applicant conducted a population PK analysis that studied the effects of concomitant medications used in the treatment of SLE on the PK parameter estimates of belimumab. No clinically relevant interactions were observed (see Pharmacokinetic section).

Vaccine substudy of C1056

The effect of belimumab on vaccinations was analyzed in a substudy of Study C1056. The prior history of having received influenza, tetanus, or pneumococcal vaccines was to be obtained from each subject during screening as part of the subject's medical history. Subjects who received an influenza vaccine within 1 year prior to Day 0 were to be tested for influenza vaccine antibody levels on the Day 0 and Week 52 visits. Subjects who received tetanus and/or pneumococcal vaccines within 5 years prior to

Day 0 were to be tested for tetanus and/or pneumococcal vaccine antibody on the Day 0 and Week 52 visits.

Levels of antibodies to S pneumoniae (anti-pneumococcal IgG) were not significantly affected by 52 weeks of treatment with belimumab. Percent changes in IgG antibodies specific to the 12 antigens tested between baseline and Week 52 were similar across the three treatment groups and the percent of subjects that had measurable specific responses to each serotype at baseline that was retained at the end of the 52-week period was also similar between active groups and placebo.

Percent changes in antibodies specific to tetanus tested between baseline and Week 52 were comparable across the 3 treatment groups. Similar to what was observed for pneumococcus, the percent of subjects that maintained a protective specific response at the end of the 52-week period was also similar between active groups and placebo.

Percent changes between baseline and Week 52 in antibodies against influenza antigens for vaccines received in 2006-2007 and 2007-2008 were generally similar across the 3 treatment groups, even though in some cases a statistically significant difference was observed between treatment groups. These differences were due to increases in titers observed during the 52 weeks of treatment even though no information identifying these subjects as being vaccinated while on study is available.

Subjects' immune responses to vaccines received during their participation in the study were also tested and the level of response compared between belimumab and placebo treatment groups. Though all subjects treated with belimumab or placebo were able to mount a protective response to pneumococcal (n=4) or tetanus (n=7) vaccines, too few subjects were vaccinated to draw conclusions.

Similarly, though a larger number of subjects (n=76) received seasonal flu vaccines while on the study, due to the presence of the same influenza strains in consecutive seasonal flu vaccines, most subjects had pre-existing antibodies in the protective range for the majority of antigens. Therefore, it was not possible to draw conclusions regarding the ability of subjects receiving belimumab to mount protective responses to flu vaccines.

Overall, the effects of belimumab with regards to immunization are not known.

Discontinuation due to adverse events

Approximately 6% to 7% of subjects in the IV SLE CRD studies discontinued treatment because of an AE, with similar rates across the placebo, 1 mg/kg and 10 mg/kg treatment groups (see table below). Similarly, approximately 13% of subjects in these groups had AEs leading to dosing interruption.

Adverse Events Leading to Study Drug Interruption or Discontinuation (IV SLE CRD Studies)

	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
At least 1 AE resulting in dosing interruption	85 (12.6%)	86 (12.8%)	25 (22.5%)	91 (13.5%)
At least 1 AE resulting in study agent discontinuation	48 (7.1%)	42 (6.2%)	4 (3.6%)	45 (6.7%)

Studies LBSL02, C1056, and C1057

Most of the AE preferred terms only occurred in one or two subjects. Most commonly, lupus nephritis resulted in the discontinuation of 8 subjects (1.2%) in the placebo group, 4 subjects in the 1 mg/kg group (0.6%) and 6 subjects in the 10 mg/kg group (0.9%).

The most common event leading to discontinuation and with a possible link to belimumab is 'infusion related reaction'. Overall, approximately 1% of subjects treated with the 10 mg/kg dose belimumab in

the IV SLE CRD studies developed an infusion reaction that led to study drug discontinuation. Some events were considered serious and even life threatening in nature (see SAE section) and required appropriate emergency management.

Post marketing experience

Belimumab received its first marketing authorisation in the US in March 2011. To date, no post-marketing experience data are available for this drug.

2.6.1. Discussion on clinical safety

Overall, the extent of exposure in this submission is considered to meet ICH recommendations.

The addition of 10 mg/kg belimumab to standard SLE therapy was generally well tolerated, although a small increase in the incidence of infections was observed. Some patients developed infusion related reactions, some of which were reminiscent of hypersensitivity reactions. The mechanism of these reactions needs to be further elucidated.

It appears possible that an adverse effect of belimumab on humoral immune response leads to an increase in the incidence of bacterial infections. Infections have been included as an identified risk in the belimumab Risk management plan and the labelling reflects relevant concerns. Infections will further be monitored in the planned post-marketing study.

Overall, a potential risk for malignancies cannot be ruled out and should be carefully followed. A post-marketing large post-marketing safety study has been included in the RMP to collect additional malignancy data over a period of at least 5 years. In addition, a cautionary statement has been included in the SPC.

Psychiatric events including depression and suicidality are included in the RMP as a potential risk. The Applicant will prospectively evaluate data on psychiatric events, including depression and suicidality, reported from ongoing and other future clinical studies, including the planned 5-year large post-marketing safety study.

The effects of belimumab with regards to immunization are not known. As a pharmacovigilance measure, the Applicant will conduct an adult vaccine study as a post-approval commitment to further investigate the impact of belimumab treatment on response to on-treatment vaccination.

The long-term safety of belimumab is currently unknown. Thus, it is not known to what degree potential concerns relating to the long-term use of immunomodulators such as risk for opportunistic infections and risk of malignancy may also apply to belimumab. Also, withdrawal and rebound effects following treatment with belimumab have not been studied in depth. This has been included in the RMP as important missing information and the Applicant will provide a plan on how to investigate these potential effects.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The addition of 10 mg/kg belimumab to standard SLE therapy was generally well tolerated, although a small increase in the incidence of infections was observed. Some patients developed infusion related reactions, some of which were reminiscent of hypersensitivity reactions. The mechanism of these reactions needs to be further elucidated. The long-term safety of belimumab is currently unknown. Thus, it is not known to what degree potential concerns relating to the long-term use of immunomodulators may also apply to belimumab.

The RMP includes numerous pharmacovigilance measures that are considered adequate to further evaluate the safety profile of belimumab in patients with SLE.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAH submitted a risk management plan.

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (Routine and Additional)	Proposed risk minimisation activities (Routine and Additional)
Identified Risks		
Infusion Reactions	Routine pharmacovigilance Evaluation of data on infusion reactions reported from ongoing and all other future clinical studies. LBSL99, HGS1006-C1066, HGS1006-C1074, HGS1006-C1070, BEL114055, BEL114054, HGS1006-C1112, Retrospective analysis of the potential correlation between the titre and isotype of endogenous anti-glycan antibodies and the type of infusion reaction reported in Studies HGS1006-C1056 and HGS1006-C1057.	Posology and method of administration statement on infusion reactions is included in Section 4.2 of the SmPC. "Benlysta treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE. Benlysta infusions should be administered by a qualified healthcare professional trained to give infusion therapy. Administration of Benlysta may result in hypersensitivity reactions and infusion reactions. Therefore, Benlysta should be administered in an environment where resources for managing such reactions are immediately available." "Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of Benlysta. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a potentially life-threatening adverse reaction." Warning and precaution statements on infusion reactions are included in Section 4.4 of the SmPC. "Administration of Benlysta may result in hypersensitivity reactions and infusion reactions. In the event of a severe reaction, Benlysta administration must be interrupted and appropriate medical therapy administered." "Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of Benlysta." "In clinical studies, serious infusion and hypersensitivity reactions affected approximately 0.9% of patients, and included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnea. Infusion reactions occurred more frequently during the first two infusions and tended to decrease with subsequent infusions." Statements on infusion reactions are included in Section 4.8 "undesirable effects" of the SmPC. "Infusion reactions and hypersensitivity: The incidence of infusion reactions and hypersensitivity reactions, occurring during or on the same day as an infusion was 17% in the group receiving Benlysta and 15% in the group receiving placebo, with 1% and 0.3%, respectively, requiring treatment discontinuation."
Hypersensitivity Reactions	Routine pharmacovigilance Evaluation of data on hypersensitivity reactions	Posology and method of administration statement on hypersensitivity reactions is

	reported from ongoing and all other future clinical studies. LBSL99, HGS1006-C1066, HGS1006-C1074, HGS1006-C1070, BEL114055, BEL114054, HGS1006-C1112 Retrospective analysis of the potential correlation between the titre and isotype of endogenous anti-glycan antibodies and the type of infusion reaction reported in Studies C1056 and C1057.	included in Section 4.2 of the SmPC. "Benlysta treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE. Benlysta infusions should be administered by a qualified healthcare professional trained to give infusion therapy. Administration of Benlysta may result in hypersensitivity reactions and infusion reactions. Therefore, Benlysta should be administered in an environment where resources for managing such reactions are immediately available" "Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of Benlysta. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a potentially life-threatening adverse reaction." Contraindication statement on hypersensitivity included in Section 4.3 of the SmPC. "Benlysta is contraindicated in patients with hypersensitivity to belimumab or to any of the excipients." Warning and precaution statements on hypersensitivity reactions are included in Section 4.4 of the SmPC. "Administration of Benlysta may result in hypersensitivity reactions and infusion reactions. In the event of a severe reaction, Benlysta administration must be interrupted and appropriate medical therapy administered." "Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of Benlysta." "In clinical studies, serious infusion and hypersensitivity reactions affected approximately 0.9% of patients, and included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnea. Infusion reactions occurred more frequently during the first two infusions and tended to decrease with subsequent infusions." Statements on hypersensitivity reactions are included in Section 4.8 "undesirable effects" of the SmPC. "Infusion reactions and hypersensitivity: The incidence of infusion reactions and hypersensitivity reactions, occurring during or on the same day as an infusion was 17% in the group receiving Benlysta and 15% in the group receiving placebo, with 1% and 0.3%, respectively, requiring treatment discontinuation."
Infections	Routine pharmacovigilance Evaluation of data on infections reported from	Warning and precaution statements on risk of infection are included in Section 4.4 of the SmPC.

	ongoing and all other future clinical studies LBSL99, HGS1006-C1066, HGS1006-C1074, HGS1006-C1070, BEL115467, BEL114055, BEL114054, HGS1006-C1112 B-cell subsets are being collected in the ongoing Phase III continuation study, C1066. Summary of the results of the analysis of B-cell data to be submitted. Planned long term safety study BEL115467/HGS1006-C1113 to evaluate the long-term safety of IV belimumab in the SLE population by assessment of the incidence of serious infections including serious opportunistic infections (including PML)	"The mechanism of action of Benlysta could increase the potential risk for the development of infections including opportunistic infections. Physicians should exercise caution when considering the use of Benlysta in patients with chronic infection or a history of recurrent infection. Patients receiving any therapy for chronic infection should not begin therapy with Benlysta. Patients who develop an infection while undergoing treatment with Benlysta should be monitored closely. The risk of using Benlysta in patients with active or latent tuberculosis is unknown" Statements on infections are included in Section 4.8 "undesirable effects" of the SmPC. "Infections: The overall incidence of infections was 70% in the group receiving Benlysta and 67% in the group receiving placebo. Infections occurring in at least 3% of Benlysta patients and at least 1% more frequently than patients receiving placebo were nasopharyngitis, bronchitis, pharyngitis, cystitis, and gastroenteritis viral. Serious infections occurred in 5% of patients receiving Benlysta or placebo. Infections leading to discontinuation of treatment occurred in 0.6% of patients receiving Benlysta and 1% of patients receiving placebo."
Potential Risks		
Malignancies	Routine pharmacovigilance Evaluation of data on malignancies reported from ongoing and all other future clinical studies LBSL99, HGS1006-C1066, HGS1006-C1074, HGS1006-C1070, BEL115467/HGS1006-C1113 BEL114055, BEL114054, HGS1006-C1112 Planned long term safety study BEL115467/HGS1006-C1113 to evaluate the long-term safety of IV belimumab in the SLE population by assessment of the incidence of malignancies excluding non-melanoma kin cancers.	A Warning and precaution statement on malignancies and lymphoproliferative disorders is included in Section 4.4 of the SmPC. "Immunomodulatory drugs may increase the risk of malignancy. At this time, limited follow-up data from clinical trials do not suggest an increased risk but this cannot be excluded. Caution should be exercised when considering belimumab therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy."
Immunogenicity	Routine pharmacovigilance MAH will continue to assess the incidence of formation of anti-belimumab antibodies using an ECL-based bridging assay in ongoing and future clinical studies; LBSL99, HGS1006-C1066, HGS1006-C1074, HGS1006-C1070, BEL114055, BEL114054, HGS1006-C1112. Immunogenicity risk will continue to be assessed to investigate possible relationships between antibody formation and treatment outcomes and adverse events.	Section 5.1 of the SmPC describes the immunogenic potential for belimumab. "Assays sensitivity for neutralizing antibodies and non-specific anti-drug antibody (ADA) are limited by the presence of active drug in the collected samples. The true occurrence of neutralizing antibodies and non-specific anti-drug antibody in the study population is therefore not known." In the two Phase III studies, 4 out of 563 (0.7%) patients in the 10 mg/kg group and 27 out of 559 (4.8%) patients in the 1 mg/kg group tested positive for persistent presence of anti-belimumab antibodies." "Among persistent-positive subjects in the Phase III trials, 1/10 (10%) , 2/27 (7%) and 1/4

		(25%) subjects in the placebo, 1 mg/kg and 10 mg/kg groups, respectively, experienced infusion reactions on a dosing day; these infusion reactions were all non-serious and mild to moderate in severity. Few patients with ADA reported serious/severe AEs. The rates of infusion reactions among persistent-positive subjects were comparable to the rates for ADA negative patients of 75/552 (14%), 78/523 (15%), and 83/559 (15%) in the placebo, 1 mg/kg and 10 mg/kg groups, respectively."
Effect on Immunisations, Including Interactions with Live Vaccines	Routine pharmacovigilance The MAH will conduct an adult vaccine study (HGS1006-C1117) to further investigation of the impact of belimumab treatment on response to on-treatment vaccination.	Warning and precaution statements on immunisations are included in Section 4.4 of the SmPC: "Live vaccines should not be given for 30 days before, or concurrently with belimumab as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving Benlysta. Because of its mechanism of action, Benlysta may interfere with the response to immunisations. The efficacy of concurrent vaccination in patients receiving Benlysta is not known. Limited data suggest that Benlysta does not significantly affect the ability to maintain a protective immune response to immunisations received prior to administration of Benlysta. In a substudy, a small group of patients who had previously received either tetanus, pneumococcal or influenza vaccinations were found to maintain protective titres after treatment with Benlysta. There are insufficient data to draw conclusions regarding the ability of subjects receiving belimumab to mount protective responses to vaccines.
Psychiatric events including depression and suicidality	Routine pharmacovigilance Evaluation of data on psychiatric events, including depression and suicidality, reported from ongoing and all other future clinical studies LBSL99, HGS1006-C1066, HGS1006-C1074, HGS1006-C1070, BEL115467/HGS1006-C1113, BEL114055, BEL114054, HGS1006-C1112 Evaluation of safety data from ongoing studies, which will include prospective assessment of suicidality in future randomized, controlled clinical trials. Planned long term safety study BEL115467/HGS1006-C1113 to evaluate the long-term safety of IV belimumab in the SLE population	Statements on psychiatric events are included in Section 4.8 "undesirable effects" of the SmPC. "Psychiatric disorders: Insomnia occurred in 7% of the group receiving Benlysta and 5% of the group receiving placebo. Depression was reported in 5% and 4% of the groups receiving Benlysta and placebo, respectively."
Important Missing Information		
Limited data in pregnant and lactating patients	Routine pharmacovigilance Evaluation of data on any pregnancies or lactation reported from ongoing and all other future clinical studies Evaluation of data on pregnancy outcomes, live birth outcomes, and infant outcomes from the planned Pregnancy Registry BEL114256/ HGS1006-C1101	Section 4.6 of the SmPC reviews the safety of belimumab in pregnancy and lactation. Women of childbearing potential/ Contraception in males and females "Women of child-bearing potential must use effective contraception during Benlysta treatment and for at least 4 months after the last treatment."

		Pregnancy "There are a limited amount of data from the use of Benlysta in pregnant women. No formal studies have been considered. Besides an expected pharmacological effect i.e., depletion of B cells, animal studies in monkeys do not indicate direct or indirect harmful effects with respect to reproductive toxicity." "Benlysta should not be used during pregnancy unless clearly necessary." Breastfeeding "It is unknown whether Benlysta is excreted in human milk or absorbed systemically after ingestion. However, belimumab was detected in the milk from female monkeys administered 150 mg/kg every 2 weeks." "Because maternal antibodies (IgG) are excreted in breast milk, it is recommended that a decision should be made whether to discontinue breast-feeding or to discontinue/Benlysta therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman."
Limited data in Elderly Patients	Routine pharmacovigilance Evaluation of safety data from future clinical studies HGS1006-C1102, BEL115467/HGS1006-C1113, BEL114054, HGS1006-C1112. A plan how to study efficacy and safety in elderly patients is to be submitted	Section 4.2 of the SmPC informs of the lack of data in elderly patients. "The efficacy and safety of Benlysta in the elderly has not been established. Data on patients >65 years are limited to <1.6% of the studied population. Therefore, the use of Benlysta in elderly patients is not recommended unless the benefits are expected to outweigh the risks. In case administration of Benlysta to elderly patients is deemed necessary, dosage adjustment is not required (see also comment under 4.4)."
No data in paediatric patients	Routine pharmacovigilance Evaluation of safety data from planned paediatric clinical study in children aged 5-17 years (BEL114055) and follow-up of patients until 10 years after their first belimumab dose	Section 4.2 of the SmPC informs of the lack of data in children below 18 years of age. " The safety and efficacy of Benlysta in children (less than 18 years of age) has not been established. No data are available.."
Long term data on B cell levels	B-cell subsets are being collected in the ongoing Phase III continuation study, C1066. Summary of the results of the analysis of B-cell data to be submitted.	Not applicable
Lack of data in SLE patients with severe active lupus nephritis or severe active CNS lupus	Routine pharmacovigilance Evaluation of safety data from planned lupus nephritis study (BEL114054)	Section 4.2 of the SmPC informs of the lack of data in severe active lupus nephritis and severe active CNS lupus. "There are no or insufficient data available on the effects of Benlysta in patients with severe active lupus nephritis or severe active central nervous system lupus. Therefore, Benlysta cannot be recommended to treat these conditions (see section 4.4)."

Lack of data on the effect of stopping treatment (treatment holidays) and risk of rebound phenomenon	Routine pharmacovigilance A plan will be submitted by December 2011	Not applicable

The CHMP, having considered the data submitted in the application, is of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

No additional risk minimisation activities were required beyond those included in the product information.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

There are currently no established regulatory tools to evaluate the efficacy of drugs for the treatment of patients with SLE. However, based on the complexity of the disease, it is agreed that a single tool might not be sufficient in the assessment of disease activity in individual patients.

Both belimumab Phase 3 trials (C1056 and C1057) achieved a significantly higher responder rate for the treatment dose applied for (10 mg/kg) compared with placebo. Belimumab treatment demonstrated beneficial effects with higher rates of reductions in disease activity in a population with involvement of vascular, musculoskeletal, immunology, and mucocutaneous organs. In study C1056, belimumab 10 mg/kg, in addition to standard therapy, yielded 9.41% (p=0.0207, OR=1.52, 95% CI= 1.07, 2.15) more responders at Week 52 as compared to standard therapy only. In study C1057, 14% (p=0.0006, OR=1.83, 95% CI= 1.30, 2.59) more responders were seen.

Analyses of SLE flare were performed according to the modified SLE Flare Index. In study C1056, no clinically relevant benefit with regard to time to first flare or frequency of flares could be shown for the recommended belimumab treatment dose. In study C1057 some benefits with regard to time to first flare and frequency of flares could be shown for the 10 mg/kg group.

Efficacy results from placebo-controlled treatment with belimumab through 18 months (76 weeks) showed a diminished response rate from 9.41% to 6.10% and the difference was no longer statistically significant.

While uncertainty remains about the robustness of the results for the primary endpoint in the overall patient population, the results of the additional analyses showed a clinically relevant treatment effect in patients with high disease activity (anti-dsDNA antibodies and low levels of C3 and/or C4). In the subset of patients with low complement (plus antiDNA-), belimumab showed similar efficacy to that seen in the overall population, but the numbers are limited to draw any conclusion. The data further

reinforce the restriction of the indication to those patients with high disease activity (e.g antiDNA+/low complement levels). A more robust benefit is seen in this subset of patients whilst limited, or even null, benefit might be expected in the population with anti-dsDNA negative and/or normal complement levels.

- Uncertainty in the knowledge about the beneficial effects.

The feasibility of describing the appropriate target population in an indication wording was discussed during an ad hoc expert meeting. In principle, the experts concurred with an indication wording that restricts the use to patients with high disease activity. Ideally disease activity should be assessed using a validated disease index rather than laboratory values. However, the proposal from the company to use laboratory tests (anti-dsDNA, low C3/C4) only to define disease activity, rather than questionnaire, was considered acceptable for the indication wording.

The effect of belimumab has only been demonstrated in a patient population with mainly musculoskeletal, vascular, mucocutaneous and haematological involvement. Whether the effect will remain in patients with involvement of vital organ/systems (cardiovascular/respiratory, CNS and renal) is unknown. The reason for not including patients with active nephritis or CNS involvement in the Phase 3 trials seems justified but does not change the fact that data in this aspect is insufficient for conclusions on belimumab effect on key target organs. A Phase 2 trial specific to lupus nephritis is planned, but does not cover for the current lack of data in more vital organ domains. Therefore, the CHMP concluded that the effect of belimumab has only been demonstrated in a patient population with mainly musculoskeletal, vascular, mucocutaneous and haematological involvement. Whether the observed modest effect would remain in patients with other key organ involvement (mainly renal and CNS) is unknown. This is clearly reflected in the labelling and a post-approval study will evaluate the efficacy and safety of belimumab in patients with severe active lupus nephritis.

There are some uncertainties concerning optimal treatment duration, maintenance doses, treatment holidays and rebound phenomenon. The absence of information has been added as important missing information in the RMP and Applicant has committed to study treatment holidays and rebound phenomenon in upcoming studies.

The chronic use of CS was high in both studies: 76% of patients in Study C1056 and 96% in Study C1057, with half of the subjects being on high CS doses, i.e. >7.5 mg/d. The CHMP questioned whether this could be considered as standard-of-care in all parts of the EU. A corresponding question was therefore asked to the ad hoc expert group. In their response, the experts acknowledged the variability of corticosteroid use across Europe. The experts were not concerned with high use of CS in the belimumab clinical trials and did not consider the pattern of CS use to impact on the ability to extrapolate the study results to the intended EU target population.

Response rates varied according to race. The observed difference in effects between races was also discussed during the ad hoc expert meeting. The issue of a possible difference in effect between races was not of concern to the experts as this was considered manageable in clinical practice. However, the experts welcomed the company’s commitment to conduct a post-approval study to address this question.

Only 1.6% of the studies population were elderly patients. Considering that in up to 15% of cases, SLE appears in patients over 55 years and that the disease course and response to treatment differs from that seen in adults, no firm conclusions regarding efficacy in elderly can be made. This is clearly reflected in the labelling.

Risks

- Unfavourable effects

In the placebo-controlled IV SLE CRD studies (i.e. primary safety population), the incidence and distribution of AEs was generally fairly similar between the placebo group and the 1 mg/kg and 10 mg/kg belimumab groups. Common events that were reported slightly more frequently in both belimumab groups compared with placebo included: nausea, diarrhoea, nasopharyngitis, bronchitis, pain in extremity, and depression. Other events that were more commonly reported in the 10 mg/kg belimumab group compared with placebo included leukopenia, pyrexia, cystitis, viral gastroenteritis, migraine, and insomnia. However, the differences in incidence between the treatment groups for these common events were small. Similarly, the incidence of SAEs in the controlled SLE studies was similarly distributed across the treatment groups.

In the long-term open-label continuation studies, the overall incidence of events did not appear to increase over time, and some events declined. Relatively few subjects discontinued because of an AE.

The adverse event data in the RA studies (secondary safety population) were consistent with the IV SLE CRD studies.

A safety concern is the occurrence of possible hypersensitivity reactions or other infusion related reactions. In the IV SLE CRD studies, 2.1% of subjects in the 10 mg/kg belimumab group had an AE that was coded as 'infusion-related reaction' compared with 1.3% in the 1 mg/kg group and 0.7% of subjects treated with placebo. Also, 0.4% of subjects in the 10 mg/kg group and 0.3% of subjects in the 1 mg/kg group had a severe infusion related reaction compared with 0.1% of subjects who received placebo.

Four subjects (0.6%) in the 10 mg/kg belimumab group in these studies experienced SAEs of infusion related reaction combined with 2 subjects (0.3%) in the 1 mg/kg group and 2 (0.3%) in the placebo group. In addition, 2 (0.3%) subjects in the 10 mg/kg and 2 (0.3%) subjects in the 1 mg/kg group had SAEs coded as anaphylactic reaction or drug hypersensitivity reaction, compared with none in the placebo group. Two of the subjects with an anaphylactic reaction also developed angioedema. All events were considered at least possibly related to study drug.

The risk of adverse infusion reactions was increased with belimumab compared with placebo. Some of the events were life-threatening in nature and required immediate and appropriate emergency room management. Overall, the incidence of serious reactions was approximately 1%, both for the 1 mg/kg and the 10 mg/kg dose. The mechanism of these reactions needs to be further elucidated and the Applicant has committed to evaluate data on infusion reactions reported from ongoing clinical trials as well as to perform a retrospective analysis of the two pivotal studies as part of the agreed RMP. A warning regarding infusion reactions and hypersensitivity is included in the SPC.

Since belimumab is a biologic agent that inhibits the survival and differentiation of B cells, additional important events were considered the risk of infection and malignancy. These events were further analyzed by the Applicant as AEs of special interest.

In the IV SLE CRD studies, the incidence of infections was generally comparable between the 1 mg/kg and 10 mg/kg belimumab treatment groups compared with placebo, with the exception of bronchitis and nasopharyngitis, which were slightly more common in the belimumab groups. The incidence of serious bronchitis was also higher for belimumab (0.4% in the 10 mg/kg group compared with 0.1% for placebo).

The incidence of sepsis was low but also somewhat higher for belimumab compared with placebo (0.7% for the 10 mg/kg group compared with 0.4% for placebo). There were five SAEs of sepsis (0.7% of subjects) in the belimumab 10 mg/kg group compared with one subject (0.1%) in the placebo group.

Overall, there were no significant differences regarding Grade 3 or Grade 4 lymphopenia, neutropenia and IgG levels between the placebo and the belimumab 1 mg/kg or 10 mg/kg groups in the controlled SLE studies. However, subjects in the belimumab groups who experienced Grade 3 or Grade 4 lymphopenia, neutropenia, or low IgM or IgG exhibited slightly higher rates of infections versus placebo and versus subjects without these abnormalities.

- Uncertainty in the knowledge about the unfavourable effects

Belimumab is a human monoclonal antibody that specifically binds and inhibits the activity of soluble human BLyS, a member of the TNF ligand superfamily. BLyS promotes B-cell differentiation, proliferation, and Ig class switching and survival. Risks that may be associated with the use of immunomodulators in general are the risk of (opportunistic) infections and the potential risk for malignancy. It is not known to what degree these potential concerns may also apply to belimumab.

In general, in the placebo-controlled IV SLE CRD studies, the incidence and distribution of AEs was generally fairly similar between the placebo group and the 1 mg/kg and 10 mg/kg belimumab groups, which would be indicative of a generally favourable safety profile. However, it is possible that the concomitant treatment with other immunosuppressants, such as corticosteroids, could have diminished the detection of certain safety signals.

A major increase in infection incidence was not observed in the belimumab studies. The number of deaths with relation to sepsis in the controlled studies was slightly higher in the belimumab groups, compared with placebo. However, a possible relationship to belimumab was not always clear. Indeed, belimumab was used as an add-on treatment to standard of care SLE therapy, which typically includes other immunosuppressant drugs. Similarly, there were a few SAEs of opportunistic infection (including two cases of CMV infection) where a possible contributory role by belimumab could not be excluded. However, these subjects received other immunosuppressive therapies as well.

A longer follow up is needed to clarify the additional risk of infection with prolonged belimumab treatment. Also, the extent of B-cell suppression with continued treatment remains to be clarified. A submitted update for the ongoing Study C1056, which included efficacy data for Week 76, showed a continued decline in B-cell subsets compared with Week 52. It is not known whether this decline eventually stabilizes with ongoing treatment.

While cases of progressive multifocal leukoencephalopathy (PML) have been reported for other immunosuppressive drugs, to date no cases have been reported for belimumab.

In addition, the efficacy and safety of vaccinations in patients treated with belimumab has not been clarified. The Applicant has committed to perform a post-approval study to assess the efficacy of concurrent vaccination in patients receiving belimumab treatment.

There were slightly more reports of psychiatric disorders in the belimumab groups compared with placebo. The differences were small but the reasons are unclear, considering that belimumab primarily acts on B cells. Long-term follow-up data will be of value to determine whether there is a signal.

No particular trends regarding malignancy were observed in the relatively short observation period of 52 weeks of controlled data. In general, it is known that the risk of malignancy is greater in patients with SLE compared with a non-SLE population. Across the Phase 2 and 3 IV SLE studies (LBSL02,

C1056, C1057, and the open-label study LBSL99), the rate of malignant neoplasms (excluding NMSC) per 100-subject years with belimumab was similar to the rate observed in a large international SLE cohort study. Overall, no conclusions can be drawn with some certainty until more and longer duration follow-up data are available.

No particular trends regarding malignancy were observed in the relatively short observation period of 52 weeks of controlled data. However, malignancies are included as a potential risk in the RMP and the incidence of malignancies will be evaluated in a post-approval safety study evaluating the long-term safety of IV belimumab in SLE patients.

Benefit-risk balance

- Importance of favourable and unfavourable effects

There is an unmet medical need for novel options in SLE treatment. No new drugs have been approved for the indication SLE in many years. While a number of treatment options are available for SLE, many patients have incompletely controlled disease, resulting in irreversible damage to internal organ system. Standard therapy includes corticosteroids, anti-malarial agents, non-steroidal anti-inflammatory drugs, cytotoxic agents and immunosuppressive or immunomodulatory agents used in cancer or transplantation, which all causes unfavorable side-effects. Consequently, a new drug providing additional disease control or presenting a more favorable safety profile would be considered of clinical value.

Alternative analyses performed for the two pivotal Phase 3 studies support a clinically relevant treatment effect of belimumab in addition to standard therapy in patients with high disease activity. A substantially increased likelihood of a treatment response has been shown for the subpopulation of patients with anti-dsDNA antibodies and low complement levels.

The addition of 10 mg/kg belimumab to standard SLE therapy was generally well tolerated, although a small increase in the incidence of infections was observed. Some patients developed infusion related reactions, some of which were reminiscent of hypersensitivity reactions. The mechanism of these reactions has not been clarified but the Applicant has committed to conduct a study as part of the RMP to further elucidate this finding. In any case, this is not considered a major obstacle against the use of belimumab if appropriate preventive measures are taken as stated in the SmPC.

Potential concerns relating to the long-term use of immunomodulators in general are the risk for (opportunistic) infections and the potential risk for malignancy. It is not known to what degree these potential concerns also apply to a compound such as belimumab. Given that SLE is a life-long illness that requires chronic treatment, identification of such risks is of great importance. The Applicant has committed to collect long-term safety data through post-approval committments.

- Benefit-risk balance

Despite improved treatment options for patients with SLE, there is still an unmet medical need in this indication for which no new medicinal products have been approved in several decades. Belimumab has shown to be effective as an add-on therapy in a subgroup of SLE patients that have a high degree of disease activity (e.g positive anti dsDNA and low complement) despite standard therapy.

The addition of 10 mg/kg belimumab to standard SLE therapy was generally well tolerated, although a small increase in the incidence of infections was observed. Some patients developed infusion related reactions, some of which were reminiscent of hypersensitivity reactions. The long-term safety of IV belimumab treatment in SLE patients will be evaluated in a large post-approval safety study. In

addition, other known and potential risks as well as important missing information are adequately reflected in the SPC and appropriate pharmacovigilance measures are included in the RMP.

The combined favourable effects of belimumab treatment are considered to outweigh the unfavourable effects.

2.8.1. Discussion on the benefit-risk balance

Results from alternative analyses support a larger effect in patients with high disease activity indicating that belimumab could be of value for some patients. Based on available data it is acknowledged that a larger and clinically relevant benefit is shown for the subpopulation of patients with high disease activity (e.g.anti-dsDNA and low complement levels). The safety profile for this subgroup of patient does not appear to be significantly different to the safety profile for the overall study population and consequently the benefit-risk is considered positive.

Overall, the study results indicate that 52 weeks belimumab treatment may provide an additional treatment benefit of value for some patients. However, considering the initial pre-specified analyses and the alternative post hoc analyses provided, the effect demonstrated for the overall study population must be considered modest: in the primary responder analyses there was only about a 10 percentage difference between treatments; the support from the analyses of the secondary endpoints is weak.

In the high activity subgroups, however, the magnitude of effect was more pronounced and supported by consistent significant results for secondary endpoints. The data on maintenance of effect was also more convincing in these subgroups. The results in patients with high disease activity are further supported by the results obtained at 52 weeks as well as 76 weeks in the responder analyses with more stringent response criteria. In addition a substantially increased likelihood of a treatment response has been shown for the subpopulation of patients with anti-dsDNA antibodies and low complement levels.

From a safety point of view, although the mechanism for hypersensitivity and infusion reactions is currently unknown, the SmPC has been appropriately strengthened and includes recommendations for premedication and proper handling of potential events should they occur.

Belimumab represents a novel concept to induce immunosuppression. Thus, uncertainty exists regarding the potential for development of malignancies, as well as other potential long-term risks such as increased risk of developing opportunistic infections, or PML. This emphasizes the need for a proper long-term follow up. This is addressed by a 5-year large post-marketing safety study which is part of the agreed RMP; in this study events of interest, including serious infections, opportunistic infections, and malignancies (including hematological malignancies) will be monitored. No increased risk of malignancy can at the current time be attributed to treatment with belimumab.

The Risk Management Plan includes infections as an identified risk. In addition to routine pharmacovigilance, the Applicant will evaluate data on infections reported from ongoing and future clinical trials; furthermore, a post-marketing safety study will be conducted to further evaluate the incidence of all-cause mortality and adverse events of special interest, which include serious infections and opportunistic infections. For the time being no additional measures are necessary to minimize and monitor risk of infection.

2.8.2. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted in the application, is of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

No additional risk minimisation activities were required beyond those included in the product information.

2.8.3. Similarity with authorised orphan medicinal products

Not applicable

2.8.4. Market exclusivity

Not applicable

2.8.5. Significance of paediatric studies

Not applicable

2.8.6. Conformity with agreed Paediatric Investigation Plan

Not applicable

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Benlysta as add-on therapy in adult patients with active autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy was favourable and therefore recommended the granting of the marketing authorisation.